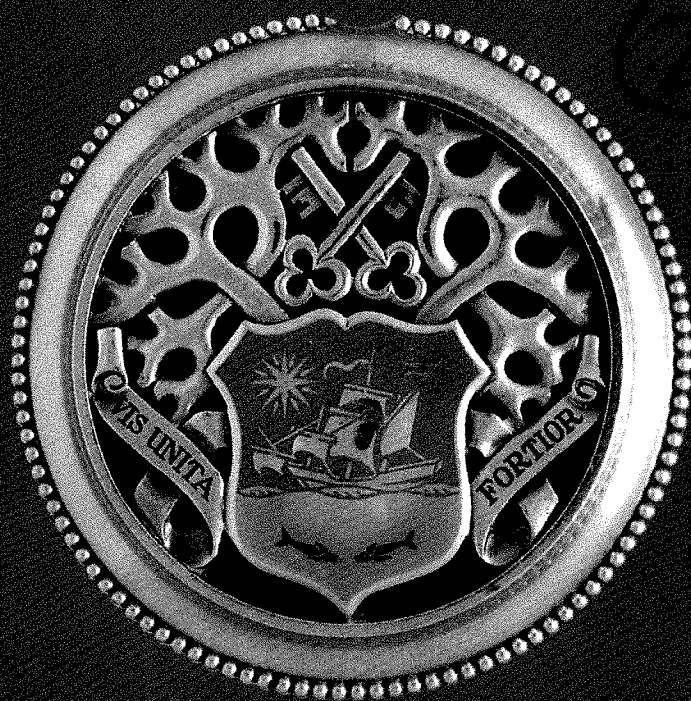


Volume 10 Supplement No 1 November 1988

British Journal of UROLOGY

**Advances in Benign Prostatic Hyperplasia and
Prostatic Carcinoma: A Perspective on Recent
Developments and Clinical Management**



**Proceedings of the International Urology Symposium
Madrid, Spain, October 31–November 3, 1988**

Churchill Livingstone

BRITISH JOURNAL OF UROLOGY

Journal of the
British Association of Urological Surgeons
and the European Society of Paediatric Urology

Editor

*G. D. CHISHOLM

Honorary Treasurer

*J. P. PRYOR

Editorial Assistant

EDNA MacDONALD

Assistant Editors

R. J. MILLARD

*J. E. NEWSAM

*R. H. WHITAKER

Editorial Committee

Chairman J. H. STEYN*

E. P. ARNOLD, Christchurch
M. HANDLEY ASHKEN, Norwich
M. BHANDARI, Lucknow
*M. C. BISHOP, Nottingham
*J. P. BLANDY, London
A. C. BUCK, Glasgow
C. A. C. CHARLTON, Bath
D. J. DU PLESSIS, Pretoria
*J. M. FITZPATRICK, Dublin
J. C. GINGELL, Bristol
J. A. GOSLING, Hong Kong
*R. R. HALL, Newcastle upon Tyne
T. B. HARGREAVE, Edinburgh
*†K. HJÄLMÄS, Gothenburg
W. F. HENDRY, London
D. KIRK, Glasgow
V. R. MARSHALL, Adelaide

*A. R. MUNDY, London
D. E. NEAL, Newcastle upon Tyne
P. H. O'REILLY, Stockport
K. F. PARSONS, Liverpool
W. B. PEELING, Newport
A. RIZVI, Karachi
*R. J. MORGAN, London
†H. J. F. R. SERUCA, Lisbon
T. SHERWOOD, Cambridge
F. P. SOONAWALLA, Bombay
D. F. M. THOMAS, Leeds
H. N. WHITFIELD, London
J. E. A. WICKHAM, London
GORDON WILLIAMS, London
*R. E. WILLIAMS, Leeds
C. R. J. WOODHOUSE, London
P. H. L. WORTH, London

*Member of Executive Committee

†Member of E.S.P.U.

Former Editors

H. P. WINSBURY-WHITE, 1929-1948
D. BAND, 1949-1966
J. D. FERGUSON, 1967-1972
W. KEITH YEATES, 1973-1977

Churchill Livingstone 

Instructions to Authors

The *British Journal of Urology* welcomes original contributions on urological subjects from all parts of the world. Papers are accepted for consideration on the understanding that their contents have not been published in whole or in part elsewhere, that they are subject to editorial revision, and that the Editor is responsible for the order of publication. Papers on nephrology, of interest to the urological surgeon, are welcome. When relevant, authors must include a statement on the ethical aspects of their research.

Manuscripts. Papers should be submitted in *Journal style*. Failure to do so may lead to significant delays in publication. Papers should be typewritten in double spacing on A4 paper (21 × 29.7 cm) with a margin of at least 3 cm all round. **Two copies of the manuscript and illustrations should be submitted** and the author should retain a copy for reference.

Authorship. All authors must give signed consent to publication. Only those who have made a substantial contribution to the work should be designated as authors and a maximum number of five is preferred. Those who have made a smaller contribution should be recognised separately in the Acknowledgements section.

Original articles should be set out as follows, with each section beginning on a separate page: title page, summary, text, references, authors' page, tables, legends to illustrations.

The *title page* should give the following information: (1) title of article, (2) initials and names of each author, (3) the department and institution to which the work should be attributed.

The *summary* should consist of very brief statements about each of the main sections.

A list of 3 to 6 *key words* should be provided.

The *text* should be arranged as follows: (1) Introduction, (2) Patients and Methods, or Materials and Methods, (3) Results, (4) Discussion and Conclusions, (5) Acknowledgements.

References. The author is responsible for the accuracy of his references. When quoted in the text they should include the author's name and year of publication. In the case of 2 authors both names should be cited. If there are more than 2 authors, only the first author plus *et al.* should be quoted. The list of references at the end of the paper should be in alphabetical order and should give the names of *all* authors unless there are more than three, when only the first three should be given followed by *et al.* With journal references the following sequence should be observed: name(s), initials, date, title of paper; name of journal abbreviated according to *Index Medicus*, volume number, first and last page numbers. Thus

Morris, J. A., Oates, K. and Staff, W. G. (1986) Scanning electron microscopy of adenomatoid tumours. *Br. J. Urol.*, **58**, 183–187.

References to books should be as follows:

Wright, F. S. and Howards, S. S. (1981). Obstructive injury. In *The Kidney*, ed. Brenner, B. M. and Rector, F. C. Second edition. Volume II. Chapter 38, pp. 2009–2044. Philadelphia: Saunders.

The *authors' page* should give the names of all authors, their qualifications and main appointment. Please indicate the name and address of the author to whom offprint requests should be made.

Tables should be kept to a minimum and laid out as simply as possible. Each should be typed on a separate sheet, numbered in Arabic numerals and should not duplicate information in the text.

Illustrations. Photographs and radiographs should be submitted in the form of half-plate prints (approximately 17 × 11 cm). All figures should be unmounted. The number of the illustration (in Arabic numerals), the author's names, and the "top" of the illustration should be indicated lightly in pencil on the back. The magnification of photomicrographs and details of staining techniques should be given. Lettering on figures must be indicated on a transparent overlay. Illustrations in colour cannot be accepted unless the author is willing to cover the cost.

Points of Technique and Case Reports should not exceed 250 words, 2 illustrations and 3 references. In **Case Reports** the sections should be (1) Case Report, (2) Comment, (3) References.

Proprietary names of drugs, instruments, etc., should be indicated by the use of initial capital letters.

Abbreviations and units. All measurements should be expressed in S.I. units except blood pressure which will continue to be expressed in mmHg. For more detailed recommendations authors may consult the Royal Society of Medicine publication entitled *Units, Symbols and Abbreviations: A guide for Biological and Medical Editors and Authors*.

Correspondence. Questions or comments concerning recently published papers may be sent to the Editor, who will refer them to the authors. The readers' comments and authors' replies may subsequently be published together in the Correspondence column.

Address. All editorial communications, including books for review, should be addressed to the Editor, Professor G. D. Chisholm, Western General Hospital, Edinburgh EH4 2XU.

Offprints. Twenty-five free offprints are supplied to the author to whom offprint requests are to be made. Order forms will be sent with the proofs for correction, all of which should be returned to the publishers within 7 days of receipt.

Subscriptions. The journal is published monthly by Churchill Livingstone. Institutional rate for 1992 is £90.00 (UK), £100.00 (overseas) or \$180.00 (USA); the Trainee rate is £39.00 (UK), £42.50 (overseas) or \$76.50 (USA) per annum, post free, for non members. Second class postage is paid at Rahway NJ Postmaster. send USA address corrections to British Journal of Urology, c/o Mercury Airfreight International Ltd Inc, 2323 Randolph Avenue, Avenel, New Jersey 07001.

Citations. This journal is indexed, abstracted and/or published on line in the following media: Adonis, Colleague (online), Current Awareness in Biological Sciences, Current Contents, Excerpta Medica, Biological Abstracts, UMI (Microfilms), BRS Colleague (full text), British Medicine, Chemical Abstracts, Modern Medicine, Index Medicus, NMLUIS Reference Up Date and UMI (Disk).

Subscription enquiries. Longman Group U.K. Limited, Subscriptions (Journals) Department, P.O. Box 77, Fourth Avenue, Harlow, Essex CM19 5BQ. Telephone: 0279 623760.

Note to Users in the USA. Authorisation to photocopy items for internal or personal use is granted by the copyright holder provided that the fee of \$2 per copy plus \$1.50 per page is paid directly to Copyright Clearance Center, 27 Congress Street, Salem, MA 01970, USA. For more information, please contact CCC. For territories outside North America, permission should be sought direct from the copyright holder. This consent does not extend to other kinds of copying, such as copying for general distribution, for advertising and promotional purposes, for creating new collective works, or for resale.

0007-1331/92/\$2 per copy \$1.50 per page

Copyright © 1992 British Journal of Urology. All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, without the prior permission of the copyright owner, or a licence permitting restricted copying in the United Kingdom issued by the Copyright Licensing Agency Ltd, 90 Tottenham Court Road, London W1P 9HE.

Printed on acid-free Fineblade Smooth 100 gsm paper. The publisher's policy is to use paper manufactured from sustainable forests.

British Journal of Urology

Volume 70 Supplement No 1 November 1992

Advancements in Benign Prostatic Hyperplasia and Prostatic Carcinoma: A Perspective on Research Developments and Clinical Management

**Proceedings of the International Urology Workshop Seville, Spain,
October 31–November 1, 1991**

Contents

Foreword	1
Terazosin in the Treatment of Benign Prostatic Hyperplasia: The United States Experience H. Lepor and A. Laddu	2
Placebo-controlled Study of Terazosin in the Treatment of Benign Prostatic Hyperplasia with 2-Year Follow-up P. Gerhard Fabricius and J. Mac Hannaford	10
Terazosin in the Treatment of Benign Prostatic Hyperplasia: A Multicentre, Placebo-Controlled Trial S. N. Lloyd, J. F. Buckley, C. P. Chilton, I. Ibrahim, A. V. Kaisary and D. Kirk	17
Use of Terazosin in the Medical Treatment of Benign Prostatic Hyperplasia: Experience in Italy F. Di Silverio	22
Future Directions in the Management of Benign Prostatic Hyperplasia S. Khoury	27
Challenges in the Management of Prostate Cancer E. D. Crawford	33
Diagnostic Challenges of Prostatic Carcinoma J. F. Jiménez-Cruz and E. Broseta	39
Postsurgical Management of the Patient Undergoing Radical Prostatectomy F. Sole-Balcels, H. Villavicencio and A. Ortiz	43
Management of Stage C Adenocarcinoma of the Prostate J. H. Lynch and C. W. Graham	50

FOREWORD

Progress in research and clinical advancements in the fields of benign prostatic hyperplasia (BPH) and prostatic cancer provided the impetus for a gathering of world-renowned specialists in urologic disease at the International Urology Workshop in Seville, Spain, on October 31–November 1, 1991. The objectives of this two-part workshop, which was sponsored by Abbott International, Ltd, were to present clinical data in BPH and in prostatic cancer, and to consider protocol design as well as outcome measurements in the context of current and future studies evaluating the various treatment modalities.

Both BPH and prostatic cancer are strongly associated with the *aging* male population. The realisation that BPH is more than a simple mechanical disease that afflicts the majority of elderly men came when investigators had identified that alpha adrenoceptors in the prostatic smooth muscle, prostatic capsule and bladder neck were responsible for the contractile properties of the prostate and, in turn, an infravesical resistance to urinary flow in the prostatic urethra. This finding subsequently led to the development of alpha blockade in the treatment of BPH. Terazosin, a selective alpha₁ adrenoceptor antagonist that relaxes the contractility of the prostate, has been studied extensively in Europe and the United States. An overview of the data emanating from clinical trials using terazosin comprised a significant portion of the workshop, given that alpha blockade represents a promising non-invasive alternative in selected patients. Other medical treat-

ments of BPH, including hormonal manipulation, were also considered in the workshop.

The rising incidence of prostate cancer has necessitated a re-evaluation of prostatic cancer screening methods and treatment modalities. Radical prostatectomy remains the gold standard of therapy for localised disease. Innovative approaches to control advanced disease, such as LHRH agonists to effect a medical castration and biological response modifiers to manage hormone-refractory cases, have merited serious study and were reviewed in addition to the more classic approaches. Stage C disease, which is not confined to the prostatic capsule yet is not metastatic, represents a challenge that will certainly spur creative techniques in future prostate cancer management.

As a derivative work of the International Urology Workshop, this supplement is intended to provide a broad perspective of the treatment trends and research opportunities that abound in the areas of BPH and prostatic cancer, with improved patient management as the ultimate goal.

William Houghton, MD
Program Moderator

Marco Caine, MS, FRCS
BPH Session Moderator

E. David Crawford, MD
Prostatic Cancer Session Moderator

November 1992

Terazosin in the Treatment of Benign Prostatic Hyperplasia: The United States Experience

H. LEPOR and A. LADDU

Departments of Urology and Pharmacology and Toxicology, Medical College of Wisconsin, Milwaukee, Wisconsin; Department of Clinical Research, Abbott Laboratories, Abbott Park, Illinois, USA

Summary—The rationale for selective α_1 blockade in benign prostatic hyperplasia (BPH) is based upon the observations that the prostate adenoma contains between 20% and 40% smooth muscle and the contractile properties of prostatic smooth muscle are mediated by the α_1 adrenoceptor. Terazosin is a selective α_1 adrenoceptor antagonist that is currently under clinical investigation for the treatment of clinical BPH. The United States experience with this drug is reviewed in the present report. The outcome measures used to assess the efficacy of terazosin in BPH includes Boyarsky symptom scores and uroflowmetry. The total Boyarsky symptom score decreased 55% and the peak urinary flow increased 47% following terazosin therapy in the cumulative open-label and single-blind studies. Three hundred and thirteen subjects with clinical BPH were randomised into a phase III double-blind parallel-group 3-month placebo-controlled study of once-a-day administration of terazosin. The total Boyarsky symptom score decreased 43% and 21% in the 10 mg and placebo treatment groups, respectively. The peak urinary flow increased 37% and 12% in the 10 mg and placebo-treated groups, respectively. The adverse events associated with terazosin were relatively minor and reversible. The United States experience has unequivocally demonstrated the short-term safety and efficacy of terazosin therapy in BPH. Studies are currently under way to determine the long-term safety and efficacy associated with terazosin therapy in BPH.

The Rationale for Alpha Antagonists in BPH

The human prostate is comprised primarily of glandular epithelium, smooth muscle and connective tissue. Benign prostatic hyperplasia represents a hyperplastic process of the stromal and epithelial elements of the prostate (Franks, 1973). Using quantitative morphometry, Bartsch *et al.* (1979) reported that the stromal:epithelial ratio in the normal prostate and in BPH was 2:1 and 5:1, respectively. Shapiro *et al.* (1992a) confirmed that the stromal:epithelial ratio is approximately 5:1 in the prostate adenoma by using computer-assisted stereology. On the basis of results obtained by quantitative morphometry, it has been determined that BPH is primarily a stromal process. Shapiro *et al.* (1992b) have described the application of double immuno-enzymatic staining and computer-assisted colour stereology to quantify the area density of

prostate smooth muscle, connective tissue and glandular epithelium. The area density of smooth muscle in the prostate adenoma ranges from 20% to 40%, depending upon the antibody used to label smooth muscle (Shapiro *et al.*, in press).

Smooth muscle represents a significant component of the human prostate. Caine *et al.* (1975) were the first investigators to characterise the physiology and pharmacology of human prostate smooth muscle. These investigators reported that the human prostate adenoma and capsule contract in the presence of norepinephrine, a non-selective adrenergic agonist. Caine recognised the therapeutic implications of pharmacologically altering the tension of prostate smooth muscle in males with symptomatic BPH (Caine *et al.*, 1976). Isometric tension studies *in vitro* subsequently demonstrated that the contractile properties of human prostate adenomas are mediated primarily by α_1 adren-

oceptors (Gup *et al.*, 1989). A relative abundance of α_1 adrenoceptors has been identified in the human prostate by use of radioligand receptor binding studies (Gup *et al.*, 1990). On the basis of the aforementioned physiological and pharmacological observations, α_1 adrenergic blockers should decrease the resistance along the prostatic urethra by relaxing the smooth muscle component of the prostate. Comparative binding and functional studies of lower genitourinary tract tissues demonstrated that α_1 adrenoceptors are sparse in the bladder body and abundant in the bladder base and prostate (Shapiro and Lepor, 1987). α_1 adrenergic antagonists are therefore ideally suited for the treatment of the dynamic component of bladder outlet obstruction because they can selectively reduce the resistance along the bladder outlet without impairing detrusor contractility.

Is there a role for alpha blockers in BPH?

Prostatectomy represents the standard therapy for symptomatic benign prostatic hyperplasia (BPH) in the United States. Prostatectomy has gained widespread acceptance for the treatment of symptomatic BPH because the procedure is relatively free of life-threatening complications and the majority of patients experience satisfactory symptomatic improvement. Transurethral prostatectomy gained widespread acceptance among the urological community without objective evidence documenting the short- and long-term effectiveness of this procedure. The absence of objective outcome assessments presumably was overlooked because there were no other effective treatment alternatives recognised for this condition. Over the past 5 years, the interest in non-surgical therapy for BPH has escalated. The quest for a non-surgical therapy has been motivated by patients seeking to avoid surgery, a federal government seeking to curtail health care expenditures, and a urologic community committed to offering patients optimal therapy.

Guidelines for the management of BPH must be based upon relative morbidity, effectiveness, and cost of surgical and non-surgical therapies. The interest in non-surgical therapy provided the impetus to define the morbidity, efficacy and cost of prostatectomy. The intra-operative and peri-operative morbidity and mortality following transurethral prostatectomy have recently been evaluated by Holtgrewe *et al.* (1989) and Mebust *et al.* (1989) (Table 1). The nature and severity of the complications following transurethral prostatectomy are not insignificant. Therefore, the decision to offer prostatectomy must reflect both the potential benefits

Table 1 Morbidity Associated with Transurethral Prostatectomy

	National survey* (%)	Mebust <i>et al.</i> † (%)
Epididymitis	4.8	1.2
UTI	8.4	2.3
Impotence	10.2	3.5
Incontinence	3.3	0.4
Transfusion	10.5	6.5
TUR syndrome	—	2.0
Death	—	0.2

* 35% of practising American urologists.

† 3885 consecutive prostatectomies at 13 institutions.

of intervention and the inherent risks associated with the procedure. Although non-surgical alternatives for the treatment of BPH are not likely to achieve the same degree of efficacy, the relative morbidity of intervention is likely to be a dominant factor favouring less invasive intervention.

It is generally accepted that transurethral prostatectomy is an effective treatment for bladder outlet obstruction secondary to BPH. The paucity of outcomes research following prostatectomy is striking. Only a few investigators have ascertained outcome following transurethral prostatectomy by using objective criteria (Hellström *et al.*, 1986; Dörflinger *et al.*, 1987; Orandi, 1987; Dörflinger *et al.*, 1988; Neal *et al.*, 1989; Lepor and Rigaud, 1990). Overall, 16% of patients do not achieve satisfactory resolution of their voiding symptoms following prostatectomy (Lepor and Rigaud, 1990). Approximately 15% of men will require a re-operation within 8 years after transurethral prostatectomy (Wennberg *et al.*, 1987). The long-term effectiveness of prostatectomy remains to be addressed. Although prostatectomy is likely to remain the most effective treatment for BPH, the limitations of this procedure provide ample justification critically to evaluate non-surgical alternatives for this condition.

Alpha blockade in BPH

Caine *et al.* (1976) were the first to report that alpha blockers were effective for the treatment of BPH. Over the past 14 years, at least 18 clinical trials evaluating alpha blockers for the treatment of BPH have been reported (Lepor, 1990). The majority of these studies were deficient in their study design because the sample sizes were small, the treatment periods were short-term, and the criteria for enrollment and assessment of efficacy were not well

defined. Phenoxybenzamine, nicergoline, thymoxamine, prazosin, alfuzosin, terazosin and YM12617 are the alpha blockers that have been evaluated for the treatment of symptomatic BPH. Sixteen of the 18 reported clinical trials confirmed Caine's original observation that alpha blockers are effective for the treatment of BPH. Phenoxybenzamine (Dibenzyl-line), prazosin (Minipress), and terazosin (Hytrin) are the alpha blockers that have been most widely investigated. A comprehensive review of all the reported clinical studies is beyond the scope of this report. The present report will review the US experience with terazosin, a selective, long-acting alpha₁ blocker.

Terazosin: a selective, long-acting alpha₁ blocker

Terazosin was the first long-acting alpha₁ adrenoceptor antagonist approved by the Food and Drug Administration (FDA) for the treatment of hypertension in the United States. The primary advantage of terazosin is that its half-life allows for a once-daily dosage regimen. Radioligand receptor binding studies have demonstrated that terazosin is highly selective for prostatic alpha₁ adrenoreceptors (Lepor *et al.*, 1988a). Isometric tension studies have demonstrated that terazosin inhibits the contractile response to phenylephrine in prostate smooth muscle via alpha₁ blockade (Lepor *et al.*, 1988b). The enantiomers of terazosin have recently been synthesised and purified (Kyncl *et al.*, 1990). Stereochemical specificity of terazosin was not observed in the prostate when binding and functional studies were used (Meretyk *et al.*, in press).

Terazosin in BPH: The US Experience

Terazosin is currently not approved by the Food and Drug Administration (FDA) for the indication of BPH. Abbott Laboratories, the manufacturer of terazosin, submitted a new drug application to the FDA in December 1991 for the use of terazosin in the treatment of BPH. Nevertheless, terazosin is widely used by American urologists for the treatment of BPH. The acceptance of terazosin has been based thus far on other investigators' experience with the drug as reported in the peer-reviewed literature. The personal experience of Lepor, two phase II studies (M87-004 and M87-006), and a phase III randomised placebo-controlled double-blind study (M87-005) are presented in this report.

Open-label and single-blind studies

Study M87-004. A total of 14 subjects participated in this single-blind phase II pilot study of once-

daily administration of terazosin to patients with symptomatic BPH. The study was conducted in 2 parts: (1) a 4-week, single-blind placebo lead-in period, and (2) a 4–10-week single-blind treatment period. The dosage of terazosin was successively increased at each study visit until either the patient was judged by the investigator to have exhibited a satisfactory clinical improvement in both subjective (symptoms) and objective (uroflowmetry) assessments, or until the maximum dose of 20 mg of terazosin had been given for 2 weeks.

Study M87-006. The study design was a multicentre, long-term, single-blind study of once-daily administration of terazosin to patients with symptomatic BPH. This study was conducted in 3 parts: (1) a 4-week placebo lead-in period, (2) an 8-week forced titration period, and (3) a maintenance period of at least 6 months. The dose of terazosin was titrated up to 10 mg. Forty-seven males were enrolled in the study.

Open-label dose titration study. Lepor *et al.* (1990a) conducted an open-label dose titration study evaluating terazosin in 45 patients with symptomatic BPH. The dose of terazosin was titrated to a maximum of 5 mg in the course of 1 month, provided that significant adverse events were not observed. The assessment of efficacy was conducted 2 months after the initiation of treatment.

Uroflowmetry. The mean baseline, change from baseline, and percentage change from baseline of the urinary flow are presented in Table 2. Overall, the peak urinary flow increased (range = 42–53%) and the mean urinary flow increased (range = 45–53%). The increase in peak and mean urinary flow was statistically significant ($P < 0.001$). It is well recognised that urinary flow is related to voided volume (Siroky *et al.*, 1979). Although there was an increase in voided volume at the final visit compared with the baseline when the results of all 3 studies were combined, the increase (range = 5–12%) was not statistically or clinically significant.

Symptom score assessment. The improvement in symptomatology was assessed by use of the Boyarsky symptom questionnaire (Boyarsky *et al.*, 1977). Overall, the mean obstructive score improved (range = 56–68%) and the mean irritative symptom score improved (range = 50–57%). The improvements in obstructive, irritative, and total symptom scores were statistically significant (Table 3).

Table 2 Uroflowmetry Following Terazosin

	Terazosin studies		
	Lepor (n=39)	004 (n=13)	006 (n=28)
Q_{max}^* (ml/s)			
Baseline	8.5	9.6	9.1
Δ	+3.6	+4.8	+4.8
% Δ	+42	+50	+53
P value	<0.001	0.010	<0.001
$Q_{mean}^\dagger$ (ml/s)			
Baseline	4.0	4.7	4.8
Δ	+1.9	+2.1	+2.5
% Δ	+48	+45	+53
P value	<0.001	<0.001	<0.001
Voided volume (ml)			
Baseline	235	311	263
Δ	+11	+30	+31
% Δ	+5	+10	+12
P value	0.592	0.358	0.205

Note: Student's *t* test was used to calculate *P* values.

* Q_{max} = maximum urinary flow.

† Q_{mean} = mean urinary flow.

Table 3 Symptoms Assessment Following Treatment with Terazosin

Symptom score	Lepor (n=39)	004 (n=13)	006 (n=37)
Obstructive*			
baseline	6.7	7.9	6.8
Δ	-4.2	-4.5	-4.7
% Δ	-63	-56	-68
P value	<0.001	<0.001	<0.001
Irritative†			
baseline	4.9	4.4	4.3
Δ	-1.7	-1.7	-1.5
% Δ	+35	-39	-35
P value	<0.001	0.004	<0.001
Total baseline	11.6	12.3	11.1
Δ	-6.6	-6.2	-6.2
% Δ	-57	-50	-55
P value	<0.001	<0.001	<0.001

Note: Student's *t* test was used to calculate *P* values.

* Obstructive symptoms: hesitancy, intermittency, terminal dribbling, impairment of size and force of urinary stream and sensation of incomplete emptying.

† Irritative symptoms: nocturia, daytime frequency, urgency and dysuria.

Blood pressure. The patients enrolled into the study reported by Lepor *et al.* (1990a) were all normotensive. The mean baseline systolic and diastolic blood pressures were 131 mm Hg and 78 mm Hg, respectively. The mean systolic blood pressure change

during treatment with 5 mg of terazosin was less than 1 mm Hg.

Adverse reactions. The adverse reactions observed in the dose titration studies may overestimate toxicity because the dose of terazosin was often titrated to the maximum tolerable dose. In the majority of patients, terazosin was titrated to a dose ≥ 10 mg. In addition, a placebo group was not available for comparison. The adverse reactions occurring with an incidence $> 5\%$ included headache (10%), asthenia (7%) and dizziness (14%). All adverse events were reversible upon termination of therapy.

Phase III randomised placebo-controlled double-blind study

Study M87-005. A total of 487 patients were enrolled into this multicentre phase III randomised placebo-controlled double-blind parallel study of once-daily administration of terazosin in the treatment of symptomatic BPH. The study was conducted in two parts: (1) a 4-week single-blind placebo lead-in period, and (2) a 12-week double-blind treatment period. The peak and mean urinary flow and Boyarsky symptom scores were evaluated at each study visit. The Boyarsky symptom questionnaire scores the frequency and severity of 9 urinary symptoms associated with BPH on a numerical scale of 0–3, with 0 indicating the absence of symptoms and 3 denoting severe symptoms (Boyarsky *et al.*, 1977). The sums of the obstructive (hesitancy, intermittency, terminal dribbling, impairment of size and force of stream, and sensation of incomplete emptying) and irritative (nocturia, daytime frequency, urgency and dysuria) symptoms yield the obstructive score and irritative score, respectively. The baseline for each efficacy parameter (urinary flow and symptom scores) was calculated as the mean of the values measured during the last 2 patient visits of the placebo lead-in period.

Patients entered the double-blind treatment period of the study after the placebo lead-in period if: (1) all screening procedures had been reviewed by the investigator and the patient satisfied all selection criteria; (2) the symptom score was ≥ 1 on at least 2 of the symptoms classified as obstructive; (3) the peak urinary flow was at least 5 ml/s but not more than 12 ml/s at each visit of the placebo lead-in period and the voided volume was at least 150 ml; and (4) the residual volume obtained by catheterisation was ≤ 200 ml. These criteria were fulfilled by the 314 patients who were entered into the double-blind treatment period. At the final

visit of the placebo lead-in period, qualifying patients were assigned to double-blind treatment with placebo or with 2, 5 or 10 mg of terazosin once daily; the assignment was made by use of a computer-generated randomisation list blocked by study site.

Of the 314 randomised patients, 252 (80%) met protocol eligibility requirements and had at least 1 evaluable symptom measurement in the maintenance period. These patients were included in the analysis of symptoms. A total of 244 (78%) had evaluable flow rate measurements and were included in the analysis of flow rates and voided volumes. Among the 4 treatment arms, there were no statistically significant differences in the mean age, body weight, height, prostate size, systolic and diastolic blood pressure, mean urinary flow, voided volume, total symptom score, irritative symptom score, obstructive symptom score, post-void residual volume and percentage of patients with detrusor instability. The mean baseline peak urinary flow was 8% higher in the placebo group than in the terazosin groups.

The Boyarsky symptom questionnaire was used as the primary measure of symptomatic improvement. The changes in obstructive, irritative and total symptom scores from baseline to the final visit are presented in Table 4. Statistically significant ($P < 0.05$) decreases from baseline in obstructive, irritative and total symptom scores were observed for all terazosin treatment groups. All terazosin treatment groups had significantly greater decreases in irritative and total scores than the placebo group.

The decreases in obstructive score for the 5 and 10 mg terazosin treatment groups were also significantly greater than those for the placebo group. The symptom score improvement was dose related. The change in total symptom scores was evaluated according to the percentage of patients experiencing >10% deterioration, 10% deterioration to 10% improvement, >10–30% improvement, >30–50% improvement, and >50% improvement. The percentage of patients experiencing >30% improvement in total symptom score in the placebo and the 2, 5, and 10 mg terazosin treatment groups was 38%, 54%, 63% and 70%, respectively. The percentage of patients experiencing >30% improvement in total symptom score in the 5 and 10 mg terazosin treatment groups was significantly greater than the percentage in the placebo group.

The changes in peak and mean urinary flow and in voided volume are presented in Table 5. A statistically significant improvement from baseline was observed in the peak and mean urinary flow for all treatment groups, including the placebo group. The 10 mg treatment group had significantly larger increases from baseline in the peak and mean urinary flow than the placebo group. The 5 mg treatment group also had a significantly larger increase in mean flow rate than the placebo group; however, the response of the 5 mg group was similar to that of the 2 mg group. The relationship between change in urinary flow and maintenance dose suggests a dose-related response. There were no significant differences among treatment groups in change from baseline for voided volume. The

Table 4 Analysis of Changes in Signs and Symptoms from Baseline to Final Visit

Variable	Treatment group	n	Baseline mean	Final visit mean	Intragroup change from baseline			Intergroup comparisons compared with placebo			Percentage change
					Mean	(SE)	P value	Mean	(SE)	P value	
Obstructive	Placebo	60	5.4	3.8	-1.6	(0.3)	<0.001				-30.2
	2 mg	68	5.8	3.5	-2.4	(0.3)	<0.001	-0.7	(0.4)	0.081	-40.4
	5 mg	65	6.2	3.4	-2.8	(0.3)	<0.001	-1.1	(0.4)	0.007	-44.7
	10 mg	59	5.7	2.6	-3.2	(0.3)	<0.001	-1.5	(0.4)	<0.001	-55.4
Irritative	Placebo	60	4.2	3.9	-0.4	(0.2)	0.046				-8.4
	2 mg	68	4.2	3.3	-0.9	(0.2)	<0.001	-0.6	(0.2)	0.023	-21.9
	5 mg	65	4.6	3.5	-1.1	(0.2)	<0.001	-0.7	(0.2)	0.004	-23.7
	10 mg	59	4.3	3.2	-1.1	(0.2)	<0.001	-0.8	(0.3)	0.003	-26.0
Total	Placebo	60	9.7	7.7	-2.0	(0.4)	<0.001				-20.7
	2 mg	68	10.0	6.8	-3.3	(0.4)	<0.001	-1.3	(0.5)	0.020	-32.7
	5 mg	65	10.8	6.9	-3.8	(0.4)	<0.001	-1.8	(0.5)	<0.001	-35.7
	10 mg	59	10.0	5.7	-4.3	(0.4)	<0.001	-2.3	(0.6)	<0.001	-42.9

Note: Results presented have been rounded out to the number of decimal places shown. Differences were calculated before the results were rounded out.

Table 5 Analysis of Changes in Flow Rates and Voided Volume from Baseline to Final Visit

Variable	Treatment group	n	Baseline mean	Final visit mean	Intragroup change from baseline			Intergroup comparisons compared with placebo			Percentage change
					Mean	(SE)	P value	Mean	(SE)	P value	
Peak (ml/s)	Placebo	58	9.7	10.8	1.2	(0.4)	0.007				11.9
	2 mg	64	8.9	11.1	2.1	(0.4)	<0.001	1.0	(0.6)	0.095	23.9
	5 mg	65	9.2	11.2	2.0	(0.4)	<0.001	0.8	(0.6)	0.164	21.4
	10 mg	57	9.0	12.3	3.3	(0.4)	<0.001	2.1	(0.6)	<0.001	36.5
Mean (ml/s)	Placebo	58	4.9	5.3	0.4	(0.2)	0.053				9.1
	2 mg	64	4.6	5.6	1.0	(0.2)	<0.001	0.5	(0.3)	0.079	21.5
	5 mg	65	4.4	5.6	1.2	(0.2)	<0.001	0.8	(0.3)	0.017	27.0
	10 mg	57	4.4	6.3	1.8	(0.2)	<0.001	1.4	(0.3)	<0.001	41.3
Voided volume (ml)	Placebo	58	263.9	278.1	14.2	(14.2)	0.319				5.4
	2 mg	64	277.8	296.1	18.3	(13.3)	0.169	4.2	(19.4)	0.821	6.6
	5 mg	65	279.6	293.5	13.9	(13.3)	0.297	-0.2	(19.5)	0.990	5.0
	10 mg	57	259.2	303.5	44.4	(14.1)	0.002	30.2	(20.0)	0.132	17.1

Note: Results presented have been rounded out to the number of decimal places shown. Differences were calculated before the results were rounded out

percentages of patients experiencing >30% increase in peak urinary flow in the placebo and the 2, 5, and 10 mg terazosin treatment groups were 25%, 36%, 35% and 58%, respectively. A significantly greater proportion of patients in the 10 mg treatment group experienced an improvement of this magnitude than in the placebo group.

Overall, the adverse events in the 4 treatment groups were minor and reversible (Table 6). Although higher frequencies of asthenia, flu syndrome and dizziness were observed in the terazosin treatment groups, the differences from placebo were not statistically significant when tested by Fisher's exact test. There was a significantly greater incidence of postural hypotension in the 5 mg terazosin group than in the placebo group. One patient in the 10 mg treatment group developed syncope. The incidence of syncope in the 10 mg treatment group was thus 1 of 79 (1.3%). The

incidence of syncope for all terazosin-treated patients was <0.5%.

An effort was made to identify clinical or urodynamic factors that would predict a favourable outcome to terazosin therapy. The relationships between percentage change in total symptom score and peak urinary flow with baseline age, prostate size, peak urinary flow, mean urinary flow, post-void residual volume, obstructive symptom score, irritative symptom score and total symptom score were examined. No significant association was observed between treatment effect and 12 baseline factors when tested by an analysis of covariance model with terms for baseline factor, treatment groups and their interaction.

Conclusions

The US experience with terazosin in BPH unequi-

Table 6 Selected Adverse Events

	Placebo (%) (n=76)	2 mg (%) (n=81)	5 mg (%) (n=79)	10 mg (%) (n=79)
Asthenia	2 (2.6)	5 (6.2)	5 (6.4)	8 (10.1)
Flu syndrome	1 (1.3)	1 (1.2)	3 (3.8)	5 (6.3)
Headache	5 (6.6)	5 (6.2)	1 (1.3)	4 (5.1)
Postural hypotension	0	2 (2.5)	6 (7.7)	4 (5.1)
Dizziness	2 (2.6)	5 (6.2)	3 (3.8)	9 (11.4)
UTI	0	0	0	3 (3.8)
Syncope	0	0	0	1 (1.3)

vocally supports the short-term efficacy and safety of this drug for the treatment of symptomatic BPH. The randomised, double-blind placebo-controlled study provides insights related to the use of terazosin in BPH. The clinical response to terazosin was dose related and the clinical response did not plateau within the dose range evaluated (2–10 mg). The dose range evaluated was not associated with severe or irreversible adverse events. On the basis of the efficacy and safety data from the fixed-dose study, the dose of terazosin in men with symptomatic BPH may be routinely titrated to 10 mg, provided that limiting adverse events do not occur. Because the incidence of certain adverse events may be dose-related, the dose should be reduced if an adverse event occurs. Studies are currently under way to evaluate the long-term efficacy of terazosin. Lepor *et al.* (in press) recently reported that the initial improvement in symptom scores observed after terazosin therapy was maintained in 72% of subjects with BPH who were followed up for a minimum of 2 years while receiving terazosin.

The differential diagnosis for the symptom complex of prostatism includes prostate cancer, bladder cancer, bladder calculi, urethral stricture and primary neurogenic bladder. The decision to treat BPH with an alpha blocker such as terazosin cannot be made solely on the basis of a cursory digital rectal examination, the severity of the symptom of prostatism and a reduced urinary flow. Therefore, a urologist should be involved in decisions related to diagnosis and treatment of BPH. The optimal candidate for alpha₁ blockade has yet to be defined. The majority of studies evaluating alpha blockers excluded those individuals with absolute indications for intervention, such as urinary retention, recurrent urinary tract infection and renal insufficiency. The efficacy and safety of terazosin suggests that men with symptomatic BPH who lack absolute indications for surgical intervention and contra-indications for alpha blockade may be offered the latter as a treatment alternative.

There are several non-surgical alternatives that are currently under investigation in the United States, including hormonal therapy, balloon dilatation of the prostate and hyperthermia (Lepor, in press). Selecting treatment for BPH will ultimately be based upon the relative efficacy, safety and cost of treatment alternatives. Because terazosin is safe, effective and relatively inexpensive, it is likely to assume a meaningful role in the treatment of BPH.

References

- Bartsch, G., Müller, H. R., Boerholzer, M. *et al.* (1979). Light microscopic stereological analysis of the normal human prostate and benign prostatic hyperplasia. *J. Urol.*, **122**, 487–491.
- Boyarsky, S., Jones, G., Paulson, D. F. *et al.* (1977). A new look at bladder neck obstruction by the Food and Drug Administration regulators: guidelines for investigation of benign prostatic hypertrophy. *Trans. Am. Assoc. Genito.-Urin. Surg.*, **68**, 29–31.
- Caine, M., Raz, S. and Ziegler, M. (1975). Adrenergic and cholinergic receptors in the human prostate, prostatic capsule and bladder neck. *Br. J. Urol.*, **47**, 193–202.
- Caine, M., Pfau, A. and Perlberg, S. (1976). The use of alpha-adrenergic blockers in benign prostatic obstruction. *Br. J. Urol.*, **48**, 255–263.
- Dorflinger, T., Øster, M., Larsen, J. F. *et al.* (1987). Transurethral prostatectomy or incision of the prostate in the treatment of prostatism caused by small benign prostates. *Scand. J. Urol. Nephrol.*, **104**, 77–81.
- Dorflinger, T., England, D. M., Madsen, P. O. *et al.* (1988). Urodynamic and histological correlates of benign prostatic hyperplasia. *J. Urol.*, **140**, 1487–1490.
- Franks, L. M. (1973). Benign prostatic hyperplasia: gross and microscopic anatomy. In: *Benign Prostatic Hyperplasia*, ed. Grayhack, J. T., Wilson, J. D. and Scherbengke, M. J. Pp. 63–89. Bethesda, Md.: National Institutes of Health.
- Gup, D. I., Shapiro, E., Baumann, M. *et al.* (1989). The contractile properties of human prostate adenomas and the development of infravesical obstruction. *Prostate*, **15**, 105–114.
- Gup, D. I., Shapiro, E., Baumann, M. *et al.* (1990). Autonomic receptors in human prostate adenomas. *J. Urol.*, **143**, 179–185.
- Hellström, P., Lukkarinen, O. and Kootturi, M. (1986). Bladder neck incision or transurethral electroresection for the treatment of urinary obstruction caused by a small benign prostate. *Scand. J. Urol. Nephrol.*, **20**, 187–192.
- Holtgrewe, H. L., Mebust, W. K., Dowd, J. B. *et al.* (1989). Transurethral prostatectomy: practice aspects of the dominant operation in American urology. *J. Urol.*, **141**, 248–253.
- Kyncl, J. J., Horrom, B. W., Nordeen, C. W. *et al.* (1990). Terazosin enantiomers. alpha adrenoceptor interaction and antihypertensive properties. *Eur. J. Pharmacol.*, **183**, 828.
- Lepor, H. Pharmacologic management of BPH. In: *Urology Annual*, ed. Rouse, S. N. Norwalk, Conn.: Appleton and Lange. In press.
- Lepor, H. (1990). Role of alpha-adrenergic blockers in the treatment of benign prostatic hyperplasia. *Prostate*, **3**(Suppl), 75–84.
- Lepor, H., Baumann, M. and Shapiro, E. (1988a). The alpha adrenergic binding properties of terazosin in the human prostate adenoma and canine brain. *J. Urol.*, **140**, 664–667.
- Lepor, H., Gup, D. I., Baumann, M. *et al.* (1988b). Laboratory assessment of terazosin and alpha-1 blockade in prostate hyperplasia. *Urology*, **32**(Suppl), 21–26.
- Lepor, H., Knapp-Maloney, G. and Sunshine, H. (1990a). A dose titration study evaluating terazosin, a selective, once-a-day α_1 -blocker for the treatment of symptomatic benign prostatic hyperplasia. *J. Urol.*, **144**, 1393–1398.
- Lepor, H., Meretyk, S. and Knapp-Maloney, G. The safety, efficacy and compliance of terazosin therapy for benign prostatic hyperplasia. *J. Urol.* (in press).
- Lepor, H. and Rigaud, G. (1990). The efficacy of transurethral resection of the prostate in men with moderate symptoms of prostatism. *J. Urol.*, **143**, 533–537.

- Mebust, W. K., Holtgrewe, H. L., Cockett, A. T. K. et al.** (1989). Transurethral prostatectomy: Immediate and postoperative complications. A cooperative study of 13 participating institutions evaluating 3,885 patients. *J Urol.*, **141**, 243–247.
- Meretyk, S., Tang, R., Shapiro, E. et al.** Alpha₁ adrenoceptor properties of terazosin HCl and its enantiomers in the human prostate and canine brain. *Prostate*, (in press).
- Neal, D. E., Ramsden, P. D., Sharples, L. et al.** (1989) Outcome of elective prostatectomy. *Br. Med. J.*, **299**, 762–767.
- Orandi, A.** (1987). Transurethral incision of prostate compared with transurethral resection of prostate in 132 matching cases. *J. Urol.*, **138**, 810–815.
- Shapiro, E. and Lepor, H.** (1987). Alpha-adrenergic receptors in canine lower genitourinary tissues: insight into development and function. *J. Urol.*, **138**, 979–983.
- Shapiro, E., Becich, M. J., Hartanto, V. et al.** (1992). The relative proportion of stromal and epithelial hyperplasia is related to the development of clinical BPH. *J. Urol.* **147**, 1293–1297.
- Shapiro, E., Hartanto, V. and Lepor, H.** (1992). Anti-desmin vs anti-actin for quantifying the area density of prostate smooth muscle. *Prostate*, **20**, 259–267.
- Shapiro, E., Hartanto, V. and Lepor, H.** Quantifying the smooth muscle content of the prostate using double-immunoenzymatic staining and color assisted image analysis. *J. Urol.*, (in press).
- Siroky, M. B., Olsson, C. A. and Krane, R. J.** (1979). The flow rate nomogram: I. Development. *J. Urol.*, **122**, 665–668.
- Wennerg, J. E., Roos, N., Sola, L. et al.** (1987). Use of claims data systems to evaluate health care outcomes: mortality and reoperation following prostatectomy. *JAMA*, **257**, 933–936.

The Authors

H. Lepor, MD, Professor, Departments of Urology and Pharmacology and Toxicology, Medical College of Wisconsin, Milwaukee.

A. Laddu, MD, former Manager, Department of Clinical Research, Abbott Laboratories, Abbott Park, Illinois, USA.

Requests for reprints to: H. Lepor, Department of Urology, Medical College of Wisconsin, 9200 West Wisconsin Avenue, Milwaukee, WI 53226, USA.

Placebo-controlled Study of Terazosin in the Treatment of Benign Prostatic Hyperplasia with 2-Year Follow-up

P. GERHARD FABRICIUS and J. MAC HANNAFORD

Department of Urology, Ludwig-Maximilians University, Munich, Germany; International Medical and Clinical Statistics Departments, Abbott Laboratories, Abbott Park, Illinois, USA

Summary—This randomised, placebo-controlled, double-blind study was performed to evaluate the efficacy and safety of once-a-day terazosin (10 mg/d) in ambulatory patients ($n=57$) with benign prostatic hyperplasia (BPH). After a 4-week placebo lead-in and a 24-week treatment period with terazosin (with both phases being single-blind), 30 patients who responded to terazosin were randomly assigned to either the terazosin or placebo treatment group for 12 weeks. During the single-blind treatment period, the peak urine flow rate increased 54% from a baseline average of 7.76 ml/s to 11.92 ml/s after terazosin administration; the mean flow rate increased 55% from a baseline of 4.90 ml/s to 7.59 ml/s; and the residual volume decreased 56% from 93.1 ml to 40.7 ml. The mean obstructive symptom score, irritative symptom score and physician global assessment score improved by 68%, 34% and 27%, respectively. All these changes were significant when compared with baseline values.

During the double-blind period, the improvement in all the variables was sustained in the terazosin group but not in the placebo group. Peak and mean urinary flow rates, and physician assessment showed significant differences at the end of the double-blind period. Adverse events occurred only during the single-blind period. The most frequently experienced events were headache ($n=6$), asthenia ($n=3$) and hypotension ($n=3$).

A follow-up study that initially included 12 patients showed no significant loss of improvement in symptoms and no change in urodynamic parameters with the 5 mg terazosin dose at 1 year. At 2 years, the 9 remaining patients showed sustained improvement and no signs of tachyphylaxis.

It is known that the prevalence of benign prostatic hyperplasia (BPH) increases from approximately 8% in the fourth decade of life to 90% in the ninth (Berry *et al.*, 1984). The condition is often associated with troublesome micturition disorders, which are related to infravesical obstruction. Surgery (open or transurethral resection) is usually indicated if these disorders are severe. However, it is not always easy to demonstrate that prostatic adenoma causes these voiding symptoms, especially in men over 60 years of age.

There are 2 components involved in the obstruction syndrome of BPH, which have been termed mechanical (or static) and dynamic (Caine, 1986a). The mechanical component is the anatomical obstruction to urine outflow caused by the hyper-

plastic prostatic tissue, and the dynamic component is the superadded factor that is caused by variations in prostatic smooth muscle tone. Because the dynamic component of BPH varies according to the level of sympathetic stimulation acting on the alpha receptors in the prostate and prostatic capsule, alpha blockers have been used to nullify this activity (Caine *et al.*, 1975).

Several reports have documented the beneficial clinical effects of the non-selective alpha blocker phenoxybenzamine (Gerstenberg *et al.*, 1980; Caine *et al.*, 1981) and the selective alpha₁ blockers prazosin and alfuzosin (Hedlund *et al.*, 1983; Martorana *et al.*, 1984; Kirby *et al.*, 1987; Jardin *et al.*, 1991) in patients with BPH. Terazosin is another selective alpha₁ blocker that resembles

prazosin in its chemical structure (Kyncl, 1986) but is a long-acting α_1 blocker. It is currently used for the treatment of hypertension. In open-label studies of the effect of once-daily terazosin on BPH, significant improvements in obstructive and irritative symptoms of BPH were reported (Cohen *et al.*, 1989; Lepor *et al.*, 1989). The current study was undertaken to evaluate the efficacy and safety of once-daily terazosin in patients with BPH in a randomised, double-blind trial. Results of this study have been published previously (Fabricius *et al.*, 1990).

Materials and Methods

Fifty-seven men from 47 to 86 years of age (mean age, 68 years) were enrolled in the study. In all cases, BPH was diagnosed by medical history, physical examination (including digital palpation of the prostate) and evaluation of obstructive and irritative symptoms. Obstructive symptoms included hesitancy, intermittent voiding, terminal dribbling, impairment of the size and force of the urinary stream and a sensation of incomplete bladder evacuation; irritative symptoms included nocturia, daytime frequency, urgency and dysuria. Patients were enrolled in the study if they were normotensive, or if they were hypertensive but not taking antihypertensive medications. Patients were also included if they had at least 2 obstructive symptoms of BPH that were of moderate or greater severity, and if their peak urine flow rates ranged from 5 to 12 ml/s at voided volumes of at least 150 ml.

Patients with histories of carcinoma of the prostate, pelvic irradiation, urethral stricture, urinary tract calculi or surgery for prostatic hyperplasia were excluded from the study. Patients with evidence of haematuria, hydronephrosis or neurogenic bladder dysfunction were also excluded, as were patients with insulin-dependent diabetes mellitus, clinically significant renal or hepatic impairment, recent histories of myocardial infarction, transient ischaemic attacks (TIAs), cerebrovascular accidents, orthostatic hypotension or syncope.

Each of the patients gave his informed consent before enrollment in the study, and the study itself was approved by the institutional review boards at the respective test centres.

Treatment schedule

The study involved an initial single-blind, 4-week placebo lead-in period, during which the patients

were seen every 2 weeks. A placebo tablet was given once daily, matching the terazosin tablet in size, shape and colour. After the lead-in period, patients were entered in a 24-week, single-blind treatment phase, during which they were given a terazosin tablet once a day. The initial daily dosage of terazosin was 1 mg, which was increased to 2 mg and then 5 mg; each dosage was given for 2 weeks. The terazosin dosage was finally increased to 10 mg/d, a level that was maintained for the remainder of the treatment phase. During the last 18 weeks of treatment, patients were seen at regular intervals.

At the end of the 24-week, single-blind treatment phase, patients who responded to terazosin entered a 12-week, double-blind, randomised withdrawal period. Patients who had responded to terazosin (as evidenced by $\geq 30\%$ increase of peak urine flow rate and a $\geq 30\%$ decrease of residual urine volume) were randomly assigned to either maintenance of their current dosage of terazosin or to administration of placebo. Patients were seen every 4 weeks during this phase.

After this period, the patients were seen every 4 months over a follow-up of 2 years and were given a dosage of 5 mg terazosin daily.

Urological variables

Uroflowmetry was performed at each visit, with the voided volume, peak flow rates and mean flow rates determined electronically. Residual volume was also measured at every visit, including at the completion of the placebo lead-in (week 4), the single-blind treatment phase (week 24), and the double-blind withdrawal period (week 36). Patient diaries describing pertinent urological events that occurred 2 days before each study visit were collected, and symptoms and physician global assessments (ratings to indicate urological variables as being within normal limits, mild, moderate or severe) were evaluated at each visit. Blood pressure, pulse rate and body weight were recorded at each visit. A urinalysis was also performed at each visit; haematology and blood chemistry studies were performed during the placebo lead-in period, after 24 and 36 weeks of treatment, and during the follow-up.

Statistical evaluation

Urine flow rates, residual urine volume, signs and symptoms of BPH, physician assessments and vital signs were analysed with paired *t*-tests during the single-blind period. Analyses of covariance were performed on the same variables during the double-

blind period. Baseline (24-week visit) data were used as the covariates.

Results

Fifty-seven patients were enrolled in the study and received terazosin during the single-blind treatment phase. Of these patients, 53 were included in an analysis of terazosin efficacy; 3 patients were excluded from the analysis because they had not met entry criteria, and 1 patient had received treatment for only 4 weeks. Thirty patients qualified for the randomised withdrawal period. Of this

group, 27 patients were included in an efficacy analysis during this phase; 2 were excluded from the analysis because they did not meet entry criteria, and 1 patient was excluded because of non-compliance.

Single-blind treatment phase

Efficacy data are summarised in Figs. 1–4 for the single-blind treatment phase. Table 1 summarises the mean results at baseline and at the final single-blind visit. Terazosin produced statistically and clinically significant increases in the peak urine flow rates and significant improvements in the

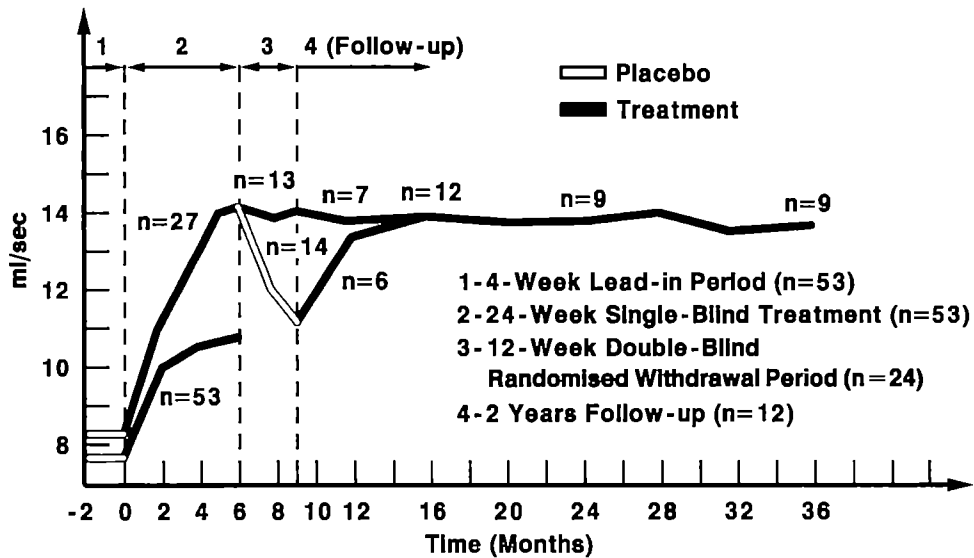


Fig. 1 Peak flow rate during single-blind and randomised withdrawal periods and 2-year follow-up.

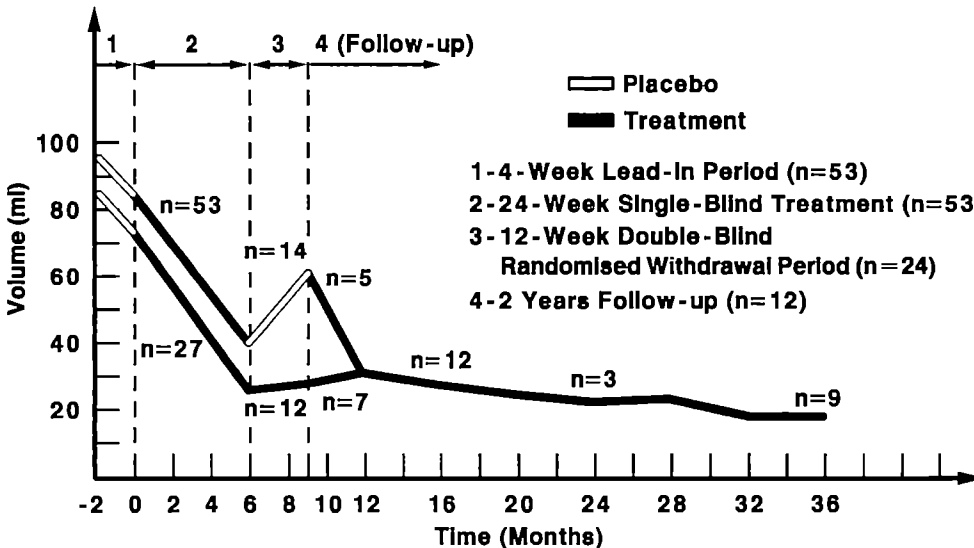


Fig. 2 Residual volume during single-blind and randomised withdrawal periods and 2-year follow-up.

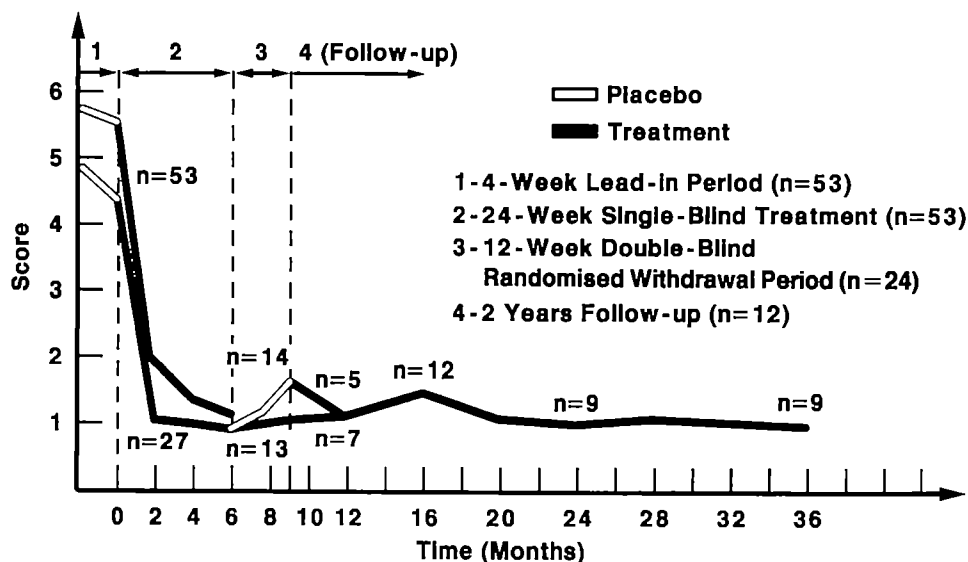


Fig. 3 Obstructive symptoms during single-blind and randomised withdrawal periods and 2-year follow-up.

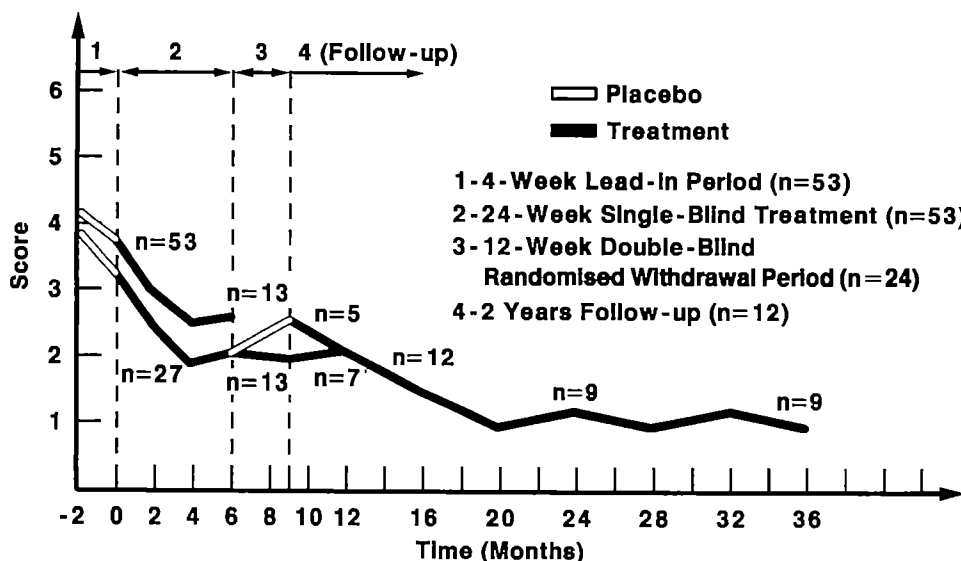


Fig. 4 Irritative symptoms during single-blind and randomised withdrawal periods and 2-year follow-up

obstructive and irritative symptom scores; these changes occurred steadily during treatment and were seen in all patients ($n=53$) initially treated with terazosin and in the patients ($n=27$) who were later randomised to receive either terazosin or placebo during the double-blind phase of the study. Figs. 1-4 show the results of terazosin treatment for all patients during the single-blind treatment phase, for the subset of patients who underwent the double-blind treatment, and for the patients who were followed up during the next 2 years.

Results of urine flow rates, residual urine volume

and obstructive and irritative symptom scores from the subset of 27 patients during both the single-blind and double-blind treatment phases are shown in Table 2. During the single-blind treatment phase, the responses of the subset to terazosin did not differ from the responses of the entire group ($n=53$) to that drug. When patients were switched to placebo during the double-blind phase, the urine flow rates, residual urine volume and obstructive and irritative symptom scores tended to revert to baseline values; with terazosin, however, improvements in these parameters were maintained.

Table 1 Effect of Terazosin on Urological Variables During the Single-Blind 24-Week Treatment Phase (n = 53)

	Mean baseline	Mean change	% Improvement
Peak flow rate (ml/s)	7.76	+4.6*	54
Mean flow rate (ml/s)	4.90	+2.69*	55
Residual volume (ml)	93.1	-52.4*	56
Obstructive symptom score	5.15	-3.51*	68
Irritative symptom score	3.70	-1.25*	34
Physician global assessment	2.68	-0.72*	27

*Significant ($P \leq 0.05$) change from baseline

Table 2 Effect of Terazosin on Urological Variables in Patients Who Underwent Randomised Withdrawal

Single-blind period					Double-blind period				
Urological variable	No. of patients	Mean baseline	Mean change	% Improvement	Treatment	No. of patients	Overall mean at 24 wk	Mean change at 36 wk	P value
Peak flow rate (ml/s)	27	8.26	+6.51*	79	Placebo	14	14.77	-4.31	0.007†
					Terazosin	13		-0.79	
Mean flow rate (ml/s)	27	5.25	+3.84*	73	Placebo	14	9.09	-2.30	0.006†
					Terazosin	13		-0.12	
Residual volume (ml)	27	84.9	-51.6*	61	Placebo	14	33.3	+22.4	0.069
					Terazosin	13		+5.6	
Obstructive symptom score	27	4.56	-3.78*	83	Placebo	14	0.78	+1.02	NS
					Terazosin	13		+0.79	
Irritative symptom score	27	3.30	-1.30*	39	Placebo	14	2.00	+0.13	NS
					Terazosin	13		-0.36	

NS, not significant.

*Significant ($P \leq 0.05$) change from baseline.

†Significant difference between groups.

There were statistically significant differences between the terazosin and placebo groups at the end of the double-blind period (week 36) for peak urine flow rate ($P \leq 0.05$). Statistically significant differences between placebo and terazosin treatment were also evident in the obstructive symptoms at week 32.

2-year follow-up

To assess the long-term efficacy and safety of terazosin, 12 patients were evaluated every 4 months. The dose of 5 mg, which was the amount of drug determined to be the best tolerated, was given every day in the evening. The 12 patients agreed to this therapy for 1 year. Symptom scores showed nearly no change and peak flow rates were the same as those seen with the 10 mg dose.

After 1 year, 2 patients who had failed to comply with the daily regimen of terazosin and had consequently experienced a worsening symptom score and flow rate underwent transurethral resection of the prostate. Another patient dropped out of the study. After 2 years, the 9 remaining patients

showed that treatment with 5 mg terazosin provided long-term improvement in symptomatic BPH (Figs 1-4).

Effect on blood pressure and heart rate

Mean systolic blood pressure, diastolic blood pressure and heart rate were decreased significantly ($P < 0.05$) from baseline to the end of the single-blind treatment phase with terazosin. Systolic blood pressure was reduced from 142 to 135 mm Hg, diastolic blood pressure was reduced from 85 to 81 mm Hg, and heart rate was reduced from 77 to 74 bpm. However, these changes were not clinically important. Body weight remained unchanged during terazosin treatment.

Safety data

There were no clinically significant changes in the haematological, blood chemistry and urological investigations. Adverse events occurred in 30% (17 of 57) of the patients, with headache (10% or 6 of 57), asthenia (5% or 3 of 57), hypotension (3%) and dysuria (3%) being the most common. None of the

adverse events necessitated dose reductions or discontinuation of the drug. No adverse events occurred during the double-blind segment of the study. However, in the long-term follow-up, the dose of terazosin was reduced from 10 mg to 5 mg to prevent dizziness.

Discussion

Benign prostatic hyperplasia is a condition of benign enlargement of the prostate gland that occurs in the aging male. Surgical removal of the prostate adenoma has been the main treatment of BPH for some time. The role of alpha blockers in the treatment of BPH was first established by Caine *et al.* (1978 and 1986a) when they reported on the use of phenoxybenzamine. Because of recent concern over the carcinogenic effect of phenoxybenzamine (Caine, 1986a, 1986b), the search for another alpha blocker to treat BPH resulted in a clinical study of prazosin (Kirby *et al.*, 1987). In addition, the frequency and severity of side effects from phenoxybenzamine, such as dizziness and asthenia, have limited the use of this drug in the treatment of BPH to a small degree (Caine *et al.*, 1981; Abrams *et al.*, 1982; Fabricius *et al.*, 1990). According to Caine *et al.* (1981), these side effects are tolerable and their incidence is acceptable, curtailing use by only 10%. Kirby *et al.* (1987) showed that prazosin improved BPH-related symptoms. However, prazosin must be administered twice daily. Terazosin is a selective alpha₁ blocker that can be administered once a day. In 2 pilot studies using open-label terazosin, Cohen *et al.* (1989) and Lepor *et al.* (1989) showed that terazosin resulted in both statistically and clinically significant improvements in the symptoms of BPH. Alpha-adrenergic blocking agents presumably reduce the smooth muscle tone of the prostate by blocking the alpha receptors in the prostate and the urethra (Furuya *et al.*, 1982; Kitada and Kumazawa, 1987).

The beneficial effects of the alpha blocker terazosin in the treatment of BPH were demonstrated during the 24-week, single-blind segment of the current study. The efficacy of terazosin was further confirmed by the results of the subsequent 12-week double-blind phase. Peak urine flow rates were significantly increased, residual urine volumes were reduced and significant improvements in both obstructive and irritative symptoms were recorded after the administration of terazosin.

The subsequent failure of placebo to sustain the beneficial effects of single-blind treatment with terazosin confirmed the usefulness of this alpha

blocker in relieving the symptoms of BPH and partially reversing the associated pathophysiological changes. Terazosin was well tolerated by normotensive patients, despite statistically significant but not clinically important decreases in the mean systolic and diastolic blood pressures and heart rate. Adverse events associated with the drug treatment were uneventful.

The long-term efficacy of terazosin was not compromised by any occurrence of tachyphylaxis. However, this treatment was only palliative and not curative. Yet without terazosin, the symptom score worsened in 2 patients. The follow-up of a small group of patients, 12 in this case, allowed no statistical analysis but did demonstrate that improvements in symptomatic BPH were safely maintained for at least 2 years in 9 patients given terazosin, and that the 5 mg once-daily dose was efficacious.

In summary, terazosin, a new selective alpha₁ blocker, is both effective and safe in relieving the symptoms of BPH. The drug is effective in increasing urine flow rate and decreasing residual urine volume when administered once a day. Additional long-term controlled studies with a greater number of patients are needed to fully evaluate the effects of terazosin in patients with BPH.

References

- Abrams, P. H., Shah, P. J. R., Stone, R. *et al.* (1982) Bladder outflow obstruction treated with phenoxybenzamine. *Br. J. Urol.*, **54**, 527-530.
- Berry, S. J., Coffey, D. S., Walsh, P. C. *et al.* (1984). The development of human benign prostatic hyperplasia with age. *J. Urol.*, **132**, 474-479.
- Caine, M. (1986a). Clinical experience with α -adrenoceptor antagonists in benign prostatic hypertrophy. *Federation Proc.*, **45**, 2604-2608.
- Caine, M. (1986b) The present role of alpha-adrenergic blockers in the treatment of benign prostatic hypertrophy. *J. Urol.*, **136**, 1-4.
- Caine, M., Perlberg, S. and Mertzyk, S. (1978). A placebo-controlled double-blind study of the effect of phenoxybenzamine in benign prostatic obstruction. *Br. J. Urol.*, **50**, 551-554.
- Caine, M., Perlberg, S. and Shapiro, A. (1981). Phenoxybenzamine for benign prostatic obstruction: review of 200 cases. *Urology*, **17**, 542-546.
- Caine, M., Raz, S. and Zeigler, M. (1975). Adrenergic and cholinergic receptors in the human prostate, prostatic capsule and bladder neck. *Br. J. Urol.*, **47**, 193-202.
- Cohen, A., Winton, L., Luther, R. *et al.* (1989). Effect of terazosin in the symptoms of benign prostatic hypertrophy (BPH). *Clin. Pharmacol. Ther.*, **45**, 183(111D-I).
- Fabricius, P. G., Weizert, P., Danzendorfer, U. *et al.* (1990). Efficacy of once-a-day terazosin in benign prostatic hyperplasia.

- sia: a randomized, double-blind placebo-controlled clinical trial. *Prostate*, 3(Suppl), 85-93.
- Furuya, S., Kumamoto, Y., Yokoyama, E. *et al.* (1982). Alpha-adrenergic activity and urethral pressure in prostatic zone in benign prostatic hypertrophy. *J. Urol.*, 128, 836-839.
- Gerstenberg, T., Blaahjerg, J., Nielsen, M. L. *et al.* (1980). Phenoxybenzamine reduces bladder outlet obstruction in benign prostatic hyperplasia: a urodynamic investigation. *Invest Urol.*, 18, 29-31.
- Hedlund, H., Andersson, K. E. and Ek, A. (1983). Effects of prazosin in patients with benign prostatic obstruction. *J. Urol.*, 130, 275-278.
- Jardin, A., Bessadoun, H., Delauche-Cavallier, M. C. *et al.* (1991). Alfuzosin for treatment of benign prostatic hypertrophy. *Lancet*, 337, 1457-1461.
- Kirby, R. S., Coppinger, S. W. C., Corcoran, M. O. *et al.* (1987). Prazosin in the treatment of prostatic obstruction: a placebo-controlled study. *Br. J. Urol.*, 60, 136-142.
- Kitada, S. and Kumazawa, J. (1987). Pharmacological characteristics of smooth muscle in benign prostatic hyperplasia and normal prostatic tissue. *J. Urol.*, 138, 158-160.
- Kyncl, J. J. (1986). Pharmacology of terazosin. *Am. J. Med.*, 80(Suppl 5B), 12-19.
- Lepor, H., Knapp-Maloney, G. and Wozniak-Petrofsky, J. (1989). The safety and efficacy of terazosin for the treatment of benign prostatic hyperplasia. *Int. J. Clin. Pharmacol. Ther. Toxicol.*, 27, 392-397.
- Martorana, G., Gilberti, C., Damonte, P. *et al.* (1984). The effect of prazosin in benign prostatic hypertrophy, a placebo controlled double-blind study. *IRCS Med. Sci.*, 12, 11-12.

The Authors

- P. G. Fabricius, MD, Senior Physician and Associate Professor, Department of Urology, Ludwig-Maximilians University, Munich, Germany.
- J. Mac Hannaford, MD, Medical Director, International Medical and Clinical Statistics Departments, Abbott Laboratories, Abbott Park, Illinois, USA.

Requests for reprints to: P. G. Fabricius, MD, Urological Clinic of the Ludwig-Maximilians University, Klinikum Grosshadern, Hospital Moabit, Turmstrasse 21, 1000 Berlin 21, Germany.

Terazosin in the Treatment of Benign Prostatic Hyperplasia: A Multicentre, Placebo-Controlled Trial

S. N. LLOYD, J. F. BUCKLEY, C. P. CHILTON, I. IBRAHIM, A. V. KAISARY and D. KIRK

Department of Urology, Western Infirmary, Glasgow; Department of Urology, Royal Infirmary, Glasgow; Department of Urology, Derbyshire Royal Infirmary, Derby; Department of Urology, Royal Free Hospital, London

Summary—The dynamic component of bladder outflow obstruction due to benign prostatic hyperplasia (BPH) has been shown to be modified by α_1 adrenergic receptors. Terazosin is an α_1 receptor-blocking agent with a long half-life permitting once-daily dosing. This drug was administered in a multicentre, randomised, placebo-controlled trial involving patients with symptomatic bladder outflow obstruction. Of 132 patients recruited for the study, 86 were randomised to receive placebo or terazosin, 81 completed the study, and 80 were considered eligible for efficacy analysis. All terazosin treatment groups showed dramatic improvement in obstructive symptoms when compared with the placebo group, but these differences were not statistically significant because of the small numbers of patients in each group. There were improvements in peak urinary flow rates, mean urinary flow rates, and residual urine volumes for the placebo and terazosin groups, but there were no statistically significant differences in the changes between the groups. Terazosin was well tolerated by patients in this study and may provide symptomatic relief in patients with BPH.

There is both an increased awareness of the prevalence of benign prostatic hyperplasia (BPH) (Garraway *et al.*, 1991) and an increased demand for the treatment of this condition. The advent of non-surgical approaches for the management of BPH has permitted symptomatic treatment in instances where surgery may not be considered appropriate—*e.g.*, in patients with lesser degrees of obstruction or in patients whose general medical condition is too debilitated. α_1 receptor-blocking agents have been shown to be effective in the management of symptoms of BPH (Iacovou and Dunn, 1987; Kirby *et al.*, 1987). Since the original observations of Caine *et al.* (1976), who showed that phenoxybenzamine acted on the dynamic component of the prostate and bladder neck, research has been directed toward developing a prostate-selective drug to reduce the unwanted effects of systemic sympathetic blockade. Terazosin (Abbott Laboratories Ltd., Queensborough, Kent) is a selective α_1 receptor-blocking agent with a

long half-life permitting once-daily dosing. The efficacy and safety of terazosin have been established in American (Lepor *et al.*, 1991) and European studies (Fabricius *et al.*, 1990). The current report details the results of a multicentre, placebo-controlled study of patients with symptomatic BPH and was carried out in the United Kingdom.

Patients and Methods

A total of 132 patients > 45 years of age (mean age, 65.7 years) was recruited from 7 centres. All patients had symptoms attributable to BPH. Criteria for entry into the study included: (1) at least 2 obstructive symptoms; (2) a peak urinary flow rate ≤ 12 ml/s with a voided volume ≥ 100 ml; and (3) a residual urine volume of < 150 ml assessed by catheterisation at visit 3.

The following conditions were regarded as reasons for exclusion of patients from the random-

isation phase of the study: prostatic cancer, urethral stricture, haematuria, prostatitis, neurogenic bladder dysfunction, bladder neck contracture, urinary tract infection, hydronephrosis, renal or hepatic impairment and diabetes mellitus. A history of pelvic irradiation, bladder neck or prostatic surgery, myocardial infarction, cerebrovascular incident or transient ischaemic attacks 6 months before the study, orthostatic hypotension, syncope, or a sitting diastolic blood pressure of >115 mm Hg also constituted reasons for exclusion. Finally, patients were also excluded if they were taking any medication that might interfere with the action of terazosin (e.g., antihypertensive medication, including diuretics or vasodilators).

All patients were seen at 2-week intervals. The protocol consisted of a 4-week placebo lead-in period (visits 1 and 2) before an 8-week double-blind randomisation period, in which patients either received placebo or terazosin administered in a 2, 5, or 10 mg dose (Fig.). Patients randomised to receive terazosin on visit 3 received a priming dose of 1 mg on the first night of treatment, followed by a 2 mg dose taken daily for 2 weeks at the approximate time of the next scheduled visit (the dose was omitted on the day of the visit). The urinary flow rate was recorded 18–30 h after the last dose of the study drug. There was a gradual dose titration for patients receiving terazosin; those randomised to receive the 2 mg dose continued on that dose, those randomised to receive the 5 mg dose did so at visit 4, and those randomised to receive the 10 mg dose first received the 5 mg dose for 2 weeks at visit 4 before receiving the 10 mg dose on visit 5.

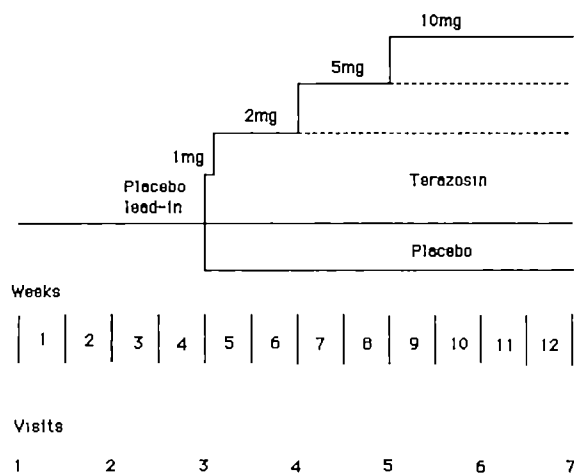


Fig. 1 Schematic diagram of trial protocol.

Full clinical examination was performed at visit 1, which was the initial screening visit, and at completion or termination of the study. Investigations performed at visit 1 and the final visit included a full blood count, renal and liver function tests, prostatic acid phosphatase determination and an electrocardiogram. At each visit, symptoms were assessed by the Boyarsky index (Boyarsky *et al.*, 1977), and the peak and mean urinary flow rates and the voided volume were recorded by a Urolyn 1000 (Dantec, Bristol). Dipstick urinalysis and urine microscopy were performed at each visit. Residual urine volume was determined at visits 3 and 7, before the filling cystometric study was performed. The patient was asked to complete a symptom diary for 2 days before his study visit. The data collected at visit 3 were taken as the baseline, and the data collected at visit 7 as the end-point of the study. In cases where data were not available for visit 7, data from visit 6 were used for analysis because the patient had received the final randomised dose for at least 2 weeks before the assessment.

One urologist reviewed all flow rate tracings without knowledge of the randomisation coding to verify computed readings. Statistical analyses of subjective and objective measurements were performed with the use of Dunnett's *t*-test (Dunnett, 1955), with a *P* value of <0.05 considered to be statistically significant.

Results

Of the 132 patients recruited to the study, 46 were subsequently excluded either because they had requested exclusion or because they had failed to fulfill the entry criteria listed previously for randomisation; in 1 instance, the study drugs were stolen. All told, 86 patients were randomised to receive placebo or terazosin. Of this group, 81 patients completed the study; however, 3 of these patients were subsequently deemed ineligible for inclusion because of protocol violation. Two patients who reached visit 6 but failed to attend visit 7 were included. This resulted in 80 patients who were eligible for efficacy analysis.

Of the patients who failed to complete the study, 4 discontinued because of adverse events during the double-blind period. Two of these patients had received 2 mg terazosin; 1 suffered a blackout and the other experienced multiple adverse events, including dysuria, frequency, dizziness and headache. Neither patient was eligible for efficacy evaluation. One patient who had been randomised

to receive 10 mg terazosin was withdrawn during the 5 mg dose titration period because of the development of congestive cardiac failure and peripheral oedema, and therefore was excluded from efficacy analysis. Another patient who received 5 mg terazosin was withdrawn because of the development of deep venous thrombosis following a fractured patella; however, because this patient had participated in the study up to visit 6, the decision was made to accept the data obtained at this visit as final for inclusion in the efficacy analysis.

One patient failed to attend visit 7; again the decision was made to accept the data from visit 6 as final for inclusion in the efficacy analysis.

Two patients randomised to receive 5 mg terazosin and 1 patient randomised to receive 10 mg terazosin completed the study but were subsequently excluded from efficacy analysis because of protocol violation, in which the timing between the ingestion of the study drugs and the recording of the urinary flow rate was incorrect.

For obstructive and irritative symptoms, improvements were seen in the mean change and mean percentage change from baseline in the placebo and terazosin groups (Tables 1 and 2), but there were no overall statistically significant differences between these groups when Dunnett's *t* test was performed. The mean improvements observed in obstructive symptoms were greater in the patients who received terazosin than in those who received placebo. For peak urinary flow rates, improvements were seen in the mean and mean percentage change from baseline recordings in the placebo and terazosin groups (Table 3), but there were no statistically significant differences between the groups. Mean urinary flow rates increased by 30% in the placebo group and by 15%, 40% and 38% in the 2, 5 and 10 mg terazosin groups, respectively. Again, there were no statistically significant differences between the groups. Evaluable residual urine volume data were only available for analysis in a third of the patients. There were small improvements in the placebo and terazosin groups, but no

Table 1 Obstructive Symptom Scores

<i>Treatment group</i>	<i>Baseline (mean ± SD)</i>	<i>Final (mean ± SD)</i>	<i>Mean change ± SD</i>	<i>Mean % change ± SD</i>	<i>P</i>
Placebo (n = 20)	6.8 ± 2.2	5.1 ± 3.6	-1.7 ± 3.6	-22.4 ± 58.1	NS
Terazosin 2 mg (n = 19)	6.5 ± 4.4	2.7 ± 2.6	-3.8 ± 3.9	-51.1 ± 54.9	NS
Terazosin 5 mg (n = 19)	6.3 ± 3.5	2.7 ± 3.1	-3.4 ± 3.5	-49.0 ± 50.1	NS
Terazosin 10 mg (n = 22)	6.6 ± 2.3	2.7 ± 2.8	-3.9 ± 3.3	-57.1 ± 41.3	NS

Table 2 Irritative Symptom Scores

<i>Treatment group</i>	<i>Baseline (mean ± SD)</i>	<i>Final (mean ± SD)</i>	<i>Mean change ± SD</i>	<i>Mean % change ± SD</i>	<i>P</i>
Placebo (n = 20)	4.4 ± 1.8	3.6 ± 1.8	-0.8 ± 1.3	-17.1 ± 32.6	NS
Terazosin 2 mg (n = 19)	4.0 ± 1.7	3.3 ± 1.7	-0.7 ± 1.7	-10.8 ± 44.0	NS
Terazosin 5 mg (n = 19)	4.1 ± 1.7	2.9 ± 1.7	-1.2 ± 1.3	-26.9 ± 35.3	NS
Terazosin 10 mg (n = 22)	5.2 ± 1.9	3.8 ± 1.9	-1.4 ± 1.9	-25.3 ± 29.1	NS

Table 3 Peak Urinary Flow Rates

<i>Treatment group</i>	<i>Baseline (mean ± SD)</i>	<i>Final (mean ± SD)</i>	<i>Mean change ± SD</i>	<i>Mean % change ± SD</i>	<i>P</i>
Placebo (n = 20)	7.8 ± 2.7	10.3 ± 3.6	2.5 ± 4.0	45.5 ± 67.1	NS
Terazosin 2 mg (n = 19)	7.9 ± 2.6	9.2 ± 3.5	1.3 ± 2.6	22.8 ± 57.1	NS
Terazosin 5 mg (n = 19)	8.0 ± 1.7	10.1 ± 3.9	2.1 ± 4.4	33.7 ± 66.7	NS
Terazosin 10 mg (n = 22)	8.4 ± 1.9	11.2 ± 2.8	2.8 ± 3.3	39.5 ± 53.9	NS

statistically significant differences between these groups.

In haematological and biochemical indices, pulse rate and blood pressure, there were no clinically significant changes from baseline. One patient who had been randomised to receive 2 mg terazosin developed electrocardiographic features of left ventricular hypertrophy that did not previously exist on the baseline tracing.

Terazosin was well tolerated during the current study, with few adverse events reported. A description of the severe events that did occur and their relationship to the study drug are presented in Table 4. Less severe side effects included dizziness and headache. Dizziness was experienced by 1 patient given placebo, 1 patient given 2 mg terazosin, 1 patient given 5 mg terazosin and 2 patients given 10 mg terazosin. Headache affected 1 patient in the placebo group, 3 patients in the 2 mg terazosin group and 1 patient in the 10 mg terazosin group.

Discussion

The current study demonstrated an improvement in mean symptom scores and mean maximum flow rates in patients receiving placebo and terazosin. There were noticeable improvements in the mean obstructive symptoms of those patients who received terazosin in comparison with those who received placebo; however, these results failed to achieve statistical significance, probably because of the small number of patients within each group. There were no statistically significant improvements in mean values for irritative symptom scores, peak urinary flow rates, mean urinary flow rates or

residual urine volumes for patients in the terazosin groups when compared with patients in the placebo group. A similar placebo response has been reported in a study investigating alfuzosin, which is another α_1 receptor-blocking agent (Jardin *et al.*, 1991).

An evaluation of the therapeutic effects that were observed with the administration of terazosin to patients with BPH in this study is complicated by the placebo effect. One possible explanation for the spontaneous improvement that was seen in urinary flow rates may be the effect of bladder training. The patient who compliantly attends a urodynamic clinic and heeds his physician's advice on how to produce a urinary flow tracing with larger voided volumes will consequently show a superior peak flow rate. Thus, the placebo effect that is often observed in BPH studies is not simply the influence of the natural history of the disease process but also the effect of optimising bladder function in bladder outflow obstruction.

Terazosin was well tolerated by the patients in this study. The greatest number of adverse events was experienced by those patients given 2 mg terazosin, probably because more patients received this dose than any other dose as a result of randomisation or titration. As a way to reduce the side effects of terazosin, administration of the drug immediately before bedtime may be recommended.

In the United Kingdom, the currently available α_1 blocking agents for the treatment of BPH are prazosin and indoramin. These 2 drugs have been shown to be statistically more effective than placebo in improving both symptoms and maximum urinary flow rates (Iacovou and Dunn, 1987; Kirby *et al.*, 1987). They are recommended for those patients requiring symptomatic relief while

Table 4 Severe Adverse Events and Relationship to Terazosin

<i>Randomised group</i>	<i>No. of patients</i>	<i>Adverse event</i>	<i>Relationship to drug*</i>
Placebo	1	Back pain	Unrelated
2 mg terazosin	1	Urinary retention	Possibly related
	1	Urinary tract infection	Possibly related
	1	Blackout	Probably related
5 mg terazosin	1	Urinary tract infection	Unrelated
	1	Dysuria	Possibly related
10 mg terazosin	1	Dysuria	Possibly related
	1	Constipation	Possibly related
	1	Dyspnoea	Possibly related
	1	Epigastric pain	Unrelated
	1	Peripheral oedema†	Probably related

*Based on the investigator's impression.

†Adverse event experienced while patient received 5 mg terazosin.

they await surgery, or for those patients considered medically unfit for surgery.

One advantage of terazosin over prazosin and indoramin is its longer half-life, permitting once-daily dosing. In a randomised, multicentre, placebo-controlled trial of 312 patients, Lepor *et al.* (1992) recently reported that terazosin in comparison with placebo resulted in a statistically significant increase in the peak flow rates and an improvement in the obstructive and irritative symptoms.

There is little dispute that the results afforded by the medical management of BPH will be inferior to those obtained by surgery in the majority of patients (Lloyd *et al.*, in press) but the indications for medical treatment are different. With the current emphasis on improved quality of life, a patient with mild BPH symptoms may wish to avoid surgery if his symptoms could be improved by a non-surgical treatment. For avoidance of the side effects associated with systemic sympathetic blockade, a prostate-selective α_1 adrenergic-blocking agent merits consideration.

Clinical studies are needed to investigate the potential benefits from combining different types of medical treatments to optimise the therapeutic effects. In the meantime, the potential benefits of bladder training and the placebo effect in patients with BPH must not be underestimated. Prostatectomy must remain the gold standard for bladder outflow obstruction secondary to BPH, but some patients may experience marked symptomatic benefit from medical therapy with drugs such as terazosin.

Acknowledgements

The authors wish to recognise the contributions of Mr M. C. Bishop, Mr E. W. Lupton and Mr D. A. Tolley. Terazosin tablets and matching placebo tablets were supplied by Abbott Laboratories Ltd., Queensborough, Kent.

References

Boyarsky, S., Jones, G., Paulson, D. F. *et al.* (1977). A new look at bladder outflow obstruction by the Food and Drug Administration regulators: guidelines for investigation of

- benign prostatic hypertrophy. *Trans. Am. Assoc. Genito-Urinary Surg.*, **68**, 29–31.
- Caine, M., Pfau, A. and Perlberg, S. (1976). The use of alpha adrenergic blockers in benign prostatic obstruction. *Br. J. Urol.*, **48**, 255–263.
- Dunnnett, C. W. (1955). A multiple comparison procedure for comparing several treatments with a control. *J. Am. Stat. Assoc.*, **50**, 1096–1121.
- Fabricius, P. G., Weizert, P., Danzendorfer, U. *et al.* (1990). Efficacy of once-a-day terazosin in benign prostatic hyperplasia: a randomised, double-blind, placebo-controlled clinical trial. *Prostate*, Suppl. 3, 85–93.
- Garraway, W. M., Collins, G. N. and Lee, R. J. (1991). High prevalence of benign prostatic hypertrophy in the community. *Lancet*, **338**, 469–471.
- Iacovou, J. W. and Dunn, M. (1987). Indoramin: an effective new drug in the management of bladder outflow obstruction. *Br. J. Urol.*, **60**, 526–528.
- Jardin, A., Bensadoun, H., Delauche-Cavallier, M. C. *et al.* (1991). Alfuzosin for treatment of benign prostatic hypertrophy. *Lancet*, **337**, 1457–1461.
- Kirby, R. S., Coppinger, S. W. C., Corcoran, M. O. *et al.* (1987). Prazosin in the treatment of prostatic obstruction: a placebo-controlled study. *Br. J. Urol.*, **60**, 136–142.
- Lepor, H., Henry, D. and Laddu, A. R. (1991). The efficacy and safety of terazosin for the treatment of symptomatic BPH. *Prostate*, **18**, 345–355.
- Lepor, H., Puras-Baez, A., Moon, T. *et al.* A randomised, placebo-controlled multicentre study of efficacy and safety of terazosin in the treatment of benign prostatic hyperplasia. *Br. J. Urol.*, in press.
- Lloyd, S. N., McMahon, A., Müller, W. *et al.* Is indoramin an effective alternative to prostatectomy? *Br. J. Urol.*, in press.

The Authors

- S. N. Lloyd, MS, FRCS, Senior Registrar in Urology, Department of Urology, Western Infirmary, Glasgow.
- J. F. Buckley, MCh, FRCSI, formerly Registrar in Urology, Royal Infirmary, Edinburgh, now Senior Registrar in Urology, Department of Urology, Royal Infirmary, Glasgow.
- C. P. Chilton, FRCS, Consultant Urologist, Department of Urology, Derbyshire Royal Infirmary, Derby.
- I. Ibrahim, MB, ChB, Research Assistant in Urology, Department of Urology, Derbyshire Royal Infirmary, Derby.
- A. V. Kaisary, ChM, FRCS, Consultant Urologist, Department of Urology, Royal Free Hospital, London.
- D. Kirk, DM, FRCS, Consultant Urologist, Department of Urology, Western Infirmary, Glasgow.

Requests for reprints to: S. N. Lloyd, Department of Urology, Western Infirmary, Dumbarton Road, Glasgow, G11 6NT

P 25892

Use of Terazosin in the Medical Treatment of Benign Prostatic Hyperplasia: Experience in Italy

F. DI SILVERIO

Department of Urology, University of Rome-La Sapienza, Rome, Italy

Summary—The purpose of this multicentre, randomised, placebo-controlled, double-blind study was to verify the safety and efficacy of terazosin, an α_1 adrenergic blocker, in patients with benign prostatic hyperplasia (BPH). This study involved 137 patients who were randomly assigned to receive either a designed dose of terazosin (2, 5 or 10 mg) or placebo. Response to treatment was measured objectively by uroflowmetric determinations. Subjective evaluation was based on the investigator's assessment of each patient's symptoms. The safety of this agent was monitored by haematological tests and urinalysis. In addition, systolic and diastolic blood pressures and pulse rates were recorded during each visit. The treatment of BPH with terazosin produced a significant improvement in mean flow rate and peak flow rate; there were no statistically significant differences in the analysis of symptomatic responses between the groups of patients treated with terazosin or placebo. Moreover, the safety of this α_1 blocker was thoroughly tested and clinically proven.

The clinical symptoms associated with benign prostatic hyperplasia (BPH) result from a combination of dynamic and mechanical obstructive components. The dynamic component involves smooth muscle tone in the prostatic urethra and capsule and its effect on infravesical resistance (Bartsch *et al.*, 1983; Berry *et al.*, 1984). The mechanical component is the physical presence of an enlarged mass of prostatic tissue.

The smooth muscle tone is dependent on the activation of α -adrenergic receptors, which are found in the bladder neck, prostatic urethra and prostatic capsule. These receptors are predominantly the α_1 type. The binding and functional properties of these adrenoceptors were studied in men with symptomatic BPH to clarify their role in the development of human prostatic disease. Moreover, Caine (1984; 1986a; 1986b) demonstrated a permanent stimulation of these receptors in BPH.

The pharmacological rationale for treating BPH with α -adrenergic blockers is based on the finding that α -adrenergic blockers relax the dynamic component. Double-blind studies have shown that both phenoxybenzamine (a non-selective α_1 and α_2 blocking agent) (Brooks *et*

al., 1983; Griffiths and Schroder, 1984; Ferrie and Paterson, 1987) and prazosin (an α -selective blocking agent) (Hedlund *et al.*, 1983; Stanaszek *et al.*, 1983) significantly improved the obstructive symptoms of BPH. Phenoxybenzamine has been associated with significant toxicity; prazosin appears to be equally effective but associated with only few side effects.

Terazosin is an α_1 adrenergic blocking agent, structurally similar to prazosin, with antihypertensive activity. Animal studies have suggested that terazosin exerts its antihypertensive effect by producing peripheral vasodilation via a blockade of α_1 adrenergic receptors (Lepor *et al.*, 1988). The advantages of terazosin are its effectiveness achieved with only once-daily dosing and its selective α_1 antagonist activity. Laboratory assessments have demonstrated that this drug completely antagonises phenylephrine-induced contractions in the human prostate (Lepor *et al.*, 1988).

To determine the safety and efficacy of terazosin in the treatment of symptomatic BPH, a multicentre, randomised, placebo-controlled, double-blind, parallel study was performed.

Patients and Methods

The study was conducted in two phases: (1) a 4-week, single-blind, placebo lead-in period, and (2) a 2-month, double-blind treatment period. The placebo lead-in period allowed us to perform baseline measurements and to identify patients who were suitable for the study. The double-blind, placebo-controlled phase of the study allowed us to evaluate the safety and efficacy of terazosin in the treatment of BPH with objective and subjective parameters. At the end of the placebo lead-in period, patients were randomly assigned to receive either a designated dose of terazosin (2, 5 or 10 mg) or placebo for the duration of the study.

Patients randomised to the terazosin group received an initial dose of 1 mg of the drug for the first day only. The patients then took a 2 mg tablet daily for the next 13 days. Patients randomised to the 2 mg dosage remained at this level for the remaining 6 weeks. Patients randomised to the 5 mg and 10 mg groups received 5 mg daily for the next 2 weeks. Then, the first group continued the 5 mg dose for the remaining 4 weeks, while the second group changed to a dose of 10 mg.

On the basis of a medical history, a physical examination (which included digital palpation of the prostate), uroflowmetric determinations and an ultrasonic measurement of prostatic size, 137 patients with BPH were randomised to receive treatment. The patients were required to be normotensive, not taking any antihypertensive medications, and to have a sitting diastolic blood pressure <115 mm Hg. The demographic data for the patients entered into screening are summarised in Table 1.

Table 1 Age (year) Distribution of Efficacy-Evaluable Randomised Patients Receiving Terazosin versus Placebo

	Placebo	Terazosin		
		2 mg	5 mg	10 mg
Mean	63.6	63.2	63.4	60.8
Minimum	46	45	47	45
Maximum	79	77	78	80

Screening examinations of the prostate by digital palpation showed that the majority of patients had moderately enlarged prostates, with no differences between the randomised treatment groups.

The response to treatment was measured objectively by uroflowmetric determinations during each

visit (every 2 weeks). Tests included measurement of peak and average flow rates. Residual urine volumes were also determined by catheterisation. For the patient to be enrolled in the study, peak flow rate had to be <12 ml/s and the voided volume had to be at least 100 ml.

Objective evaluation of response was based on changes in the urine flow rate over baseline. Subjective evaluation of response was based on the investigator's global assessment of each patient's symptoms. Symptoms were assessed with the use of methods recommended by the Food and Drug Administration (FDA); these methods were also delineated by Boyarsky *et al.* (1977).

The safety of the treatment was monitored by haematological tests and urinalysis. In addition, systolic and diastolic blood pressures and pulse rates were recorded during each visit.

Statistical plan

The efficacy of treatment was evaluated by statistical procedures. Peak and average urinary flow rates were the primary efficacy variables. Changes in peak and average urinary flow rates from baseline in the 3 groups of patients receiving terazosin were compared with rates in the placebo group by the use of Dunnett's *t* test with a significance level of $P=0.05$. The 3 groups receiving terazosin were also compared with the placebo group by the use of the least squares means at the 5% level. Changes in residual urine volume from baseline to the end of treatment were similarly analysed. Safety was evaluated by blood pressure measurements, pulse rates, laboratory test results and the patients' reports of adverse events.

Results

A total of 162 patients were enrolled in the study during the screening visit. Of these, 25 (15%) were not randomised to receive treatment; therefore, they are not included in the analyses of safety and efficacy in Table 2.

Table 2 Distribution and Evaluability Status of 137 Randomised Patients Enrolled During Screening Visit

Treatment group	No. randomised	No. (%) evaluable for efficacy	No. not evaluable
Placebo	35	32 (91)	3
Terazosin, 2 mg	34	32 (94)	2
Terazosin, 5 mg	36	34 (94)	2
Terazosin, 10 mg	32	30 (94)	2

Peak flow rate

At baseline, there was no statistically significant difference in mean peak flow rate between the treatment groups. The mean peak flow rates at baseline (V3) and the final visit (V7), and the mean change from baseline are summarised in Table 3. An analysis of the mean change from baseline showed no differences between the treatment groups overall ($P=0.068$, F test).

Table 3 Summary of Uncorrected Mean Peak Flow Rates (ml/s) for Efficacy-Evaluable Patients at Baseline (V3) and Final Visit (V7), and Mean Change from Baseline

Treatment group	V3	V7	Mean change	Mean change (%)
Placebo	8.8	10.0	1.2	16.6
Terazosin, 2 mg	8.8	11.1	2.4	32.5
Terazosin, 5 mg	8.3	11.2	2.9	39.4
Terazosin, 10 mg	8.4	10.8	2.4	32.2

There was a significant difference in the least squares means (at the 5% level without adjustment for multiple testing) between placebo and 5 mg terazosin ($P=0.012$, *t* test). There was no evidence of a difference between the treatments in percentage change from baseline ($P=0.110$, F test). There was a significant difference in the least squares means between placebo and 5 mg terazosin. The percentage change in the placebo group was higher than would be expected (17%), and although the percentage change in the terazosin groups was twice that seen in the placebo group (*i.e.*, 34%), there was no statistically significant difference between them.

Mean flow rate

There was no statistically significant difference between the treatment groups at baseline in mean flow rate ($P=0.491$, F test). Mean values for mean flow rate at baseline (V3), visit 7 (V7), and the change from baseline are summarised in Table 4.

Table 4 Summary of Uncorrected Mean Flow Rates (ml/s) for Efficacy-Evaluable Patients at Baseline (V3) and Final Visit (V7), and Mean Change from Baseline

Treatment group	V3	V7	Mean change	Mean change (%)
Placebo	4.8	5.3	0.4	13.5
Terazosin, 2 mg	4.7	5.7	1.0	28.4
Terazosin, 5 mg	4.4	5.8	1.4	35.1
Terazosin, 10 mg	4.4	6.0	1.7	45.7

The change from baseline to final visit was significantly different between treatments ($P=0.042$, F test), and Dunnett's *t* test showed a significant difference between placebo and 10 mg terazosin ($P<0.05$). There was a significant difference in the least squares means between placebo and 5 mg terazosin ($P=0.031$), and between placebo and 10 mg terazosin ($P=0.007$, *t* test).

Total volume

There was no statistically significant difference between the treatment groups at baseline in the total volume of urine voided, nor were there significant differences in mean change from baseline or percentage change between the treatments.

Residual volume

There was no statistically significant difference between the treatment groups in residual volume at baseline ($P=0.461$, F test) (Table 5). Residual volume at the final visit was less than the baseline in all treatment groups, and the greatest reduction was noted in the groups receiving 2 and 10 mg terazosin. However, there was no statistically significant difference between the groups in mean change ($P=0.229$) or percentage change ($P=0.386$, F test).

Table 5 Summary of Mean Residual Volume (ml) for Efficacy-Evaluable Patients at Baseline (V3) and Final Visit (V7), and Mean Change from Baseline

Treatment group	V3	V7	Mean change	Mean change (%)
Placebo	48.8	41.6	-7.2	-5.1
Terazosin, 2 mg	45.6	26.6	-19.0	-32.2
Terazosin, 5 mg	47.2	29.0	-18.2	-15.7
Terazosin, 10 mg	60.4	40.1	-21.7	-32.5

Obstructive symptoms score

The mean and percentage change in overall obstructive symptom score was comparable in each treatment group, and the score decreased in all groups. There was no statistically significant difference between treatments in change from baseline ($P=0.747$, F test) (Table 6).

Irritative symptoms score

There was no significant difference between the treatment groups in mean total score for irritative symptoms at baseline ($P=0.393$). The overall symptom score decreased in all groups (most notably in the group receiving 10 mg terazosin),

Table 6 Summary of Mean Total Score for Obstructive Symptoms in Efficacy-Evaluable Patients at Baseline (V3) and Final Visit (V7), and Mean Change from Baseline

Treatment group	V3	V7	Mean change	Mean change (%)
Placebo	6.0	2.6	-3.4	-57.6
Terazosin, 2 mg	5.1	1.9	-3.2	-62.1
Terazosin, 5 mg	6.0	2.5	-3.4	-60.1
Terazosin, 10 mg	6.0	2.2	-3.8	-68.5

but there was not a statistically significant difference.

The adverse event analysis revealed no unexpected or serious events attributable to the terazosin dosages used in the study. Only 1 event (a case of acute urinary retention) in the 5 mg randomisation group was considered to be severe. The laboratory data, blood pressure measurements and pulse rates were unremarkable and showed no significant changes during treatment. As would be expected in a predominantly normotensive population, the change from baseline blood pressure was small.

Discussion

This study evaluated the safety and efficacy of administering different doses of terazosin to patients with BPH. Results showed that treatment with 5 mg and 10 mg terazosin produced significant improvement in the final mean and peak flow rates when compared with the baseline. There was no statistically significant difference in the analysis of symptomatic responses between the groups of patients treated with either terazosin or placebo. However, there was evidence of a highly significant difference in results among the various investigators, and this difference was consistently present until the final visit ($P=0.010$). This finding may result from the subjective nature of the measurements, which are often subject to individual interpretation.

The safety of terazosin was thoroughly tested and clinically proven. In general, the toxicity associated with the various alpha adrenergic blockers has been highly variable. However, the adverse reactions associated with non-selective blockers (e.g., phenoxylbenzamine), are greater in incidence and severity than those of selective alpha blockers (e.g., terazosin and prazosin).

Dunzendorfer (1988) demonstrated the safety and efficacy of terazosin after 4 months of treatment when he described a 48% reduction in the obstructive

and irritative symptom scores. Results obtained on urinary flow examinations revealed a significant improvement in mean and peak flow rates (47% and 31%, respectively).

The efficacy of other alpha-adrenergic blockers in relieving the symptoms of BPH has been evaluated. Caine (1984) has reported a significant reduction in both irritative and obstructive symptoms with dibenzylamine. This drug, in doses of 10–20 mg/d, improves maximal and mean flow rates, and decreases residual urine. An objective evaluation of responses showed a reduction in daytime frequency and nocturia.

Additional studies on the use of prazosin have described an improvement in uroflowmetric measurements without any effects on frequency and urgency. Kirby *et al.* (1987) reported a randomised, placebo-controlled study evaluating prazosin in 80 patients with BPH, in which an increase of 60% was seen in the mean maximum flow rate. No adverse reactions were observed in the prazosin-treated group.

Investigators using alfuzosin, a new alpha₁ blocker, have reported improvements in mean and peak flow rates (37.8% and 27.5%, respectively) after 8 weeks of treatment (9 mg/d). Patients treated with this drug also experienced a 50% decrease in urethral pressure (Bensadoun *et al.*, 1987; Cramer *et al.*, 1988).

Conclusion

This clinical study and others reported in the literature suggest that alpha-receptor blockade may be useful in treating patients who have moderate obstructive symptoms due to BPH. This type of treatment cannot act on the mechanical component of BPH (*i.e.*, cannot modify prostatic size). However, its symptomatic activity (*i.e.*, relaxation of the smooth muscle tone in the prostatic capsule, bladder neck and prostatic urethra) succeeds in improving urine pressure-flow measurement (Di Silverio and Petrangeli, 1986; Geller, 1989).

The use of alpha-adrenergic blockade in combination with androgen withdrawal to decrease the size of the prostate could prove to be a maximally effective medical therapy for BPH. What must be clarified is a definitive role for alpha₁ blockers in the treatment of BPH. To date, a definitive long-term experience has not been reported. Future studies must identify the clinical and urodynamic parameters that will predict a favourable response to these agents.

Acknowledgements

I thank my co-workers G D'Eramo, A. Sciarra, E. Frascaro and L. Wongmer. I also thank the other investigators involved in this study: Dr Zappasodi, Professor Tenaglia, Drs Garzilli, Naccarato, Putti, Miuto and Lentini and Professor Bondolfi.

References

- Bartsch, G., Daxenbichler, G. and Rohr, H. P. (1983). Correlative morphological and biochemical investigations on the stromal tissue of the human prostate. *J. Steroid Biochem.*, **19**, 147–154.
- Beasadoun, H., Brossel, S., Jardin, A. *et al.* (1987). Etude de l'efficacité de l'alfuzosine sur la symptomatologie de l'hypertrophie bénigne de la prostate. In: Program and abstracts of the 81st Congress Français d'Urologie, 1987, Paris, France.
- Berry, J. S., Coffey, S. D., Walsh, C. P. *et al.* (1984). The development of human benign prostatic hyperplasia with age. *J. Urol.*, **132**, 474.
- Boyaraky, S., Jones, G., Paulson, D. F. *et al.* (1977). A new look at bladder neck obstruction by the Food and Drug Administration Regulators: guidelines for investigation of benign prostatic hypertrophy. *Trans. Am. Assoc. Genito-Urinary Surg.*, **68**, 29–32.
- Brooks, M. E., Sidi, A. A., Hanani, Y. *et al.* (1983). Ineffectiveness of phenoxybenzamine in treatment of benign prostatic hypertrophy: a controlled study. *Urology*, **21**, 474–478.
- Caine, M. (1984). Alpha-adrenergic blockers for the symptomatic relief of benign prostatic obstruction. *Geriatr. Med. Today*, **3**, 79–85.
- Caine, M. (1986a). Clinical experience with alpha-adrenoceptor antagonists in benign prostatic hypertrophy. *Fed. Proc.*, **45**, 2604–2608.
- Caine, M. (1986b). The present role of alpha-adrenergic blockers in the treatment of benign prostatic hypertrophy. *J. Urol.*, **136**, 1–4.
- Cramer, P., Neveux, E., Colle, M. *et al.* (1988). Etude urodynamique d'un nouvel alphabloquant, l'alfuzosine, administrée par voie intraveineuse dans les dysuries neurologiques. Presented at the 11th Congress of the Société Internationale Francophone d'Urodynamique, 1988, Montreal, Canada. Abstract 23.
- Di Silverio, F. and Petrangeli, E. (1986). Androgen and progesterone receptors in the human hyperplasia: effect of antiandrogenic treatment. *J. Steroid Biochem.*, **25** (Suppl), 356.
- Dunendorfer, U. (1988). Clinical experience: symptomatic management of BPH with terazosin. *Urology*, **32**, 27–31.
- Ferrie, B. G. and Paterson, P. J. (1987). Phenoxybenzamine in prostatic hypertrophy: a double-blind study. *Br. J. Urol.*, **59**, 63–65.
- Geller, J. (1989). Overview of benign prostatic hypertrophy. *Urology*, **34** (Suppl), 57–62.
- Griffiths, D. J. and Schroder, F. H. (1984). Phenoxybenzamine in prostatic obstruction. *Urol. Int.*, **39**, 241–242.
- Hedlund, H., Andersson, K. E. and Ek, A. (1983). Effects of prazosin in patients with benign prostatic obstruction. *J. Urol.*, **130**, 275–278.
- Kirby, R. S., Coppinger, S. W., Corcoran, M. O. *et al.* (1987). Prazosin in the treatment of prostatic obstruction: a placebo controlled study. *Br. J. Urol.*, **60**, 136.
- Lepor, H., Gup, D. L., Baumann, M. *et al.* (1988). Laboratory assessment of terazosin and alpha 1 blockade in the prostatic hyperplasia. *Urology*, **32** (Suppl), 21–26.
- Stanaszek, W. F., Kellerman, D., Brodgen, R. N. *et al.* (1983). Prazosin update: a review of its pharmacological properties and therapeutic use in hypertension and congestive heart failure. *Drugs*, **25**, 339–384.

The Author

F. Di Silverio, MD, Professor and Chair, Department of Urology

Requests for reprints to: Professor F. Di Silverio, Chair, Department of Urology "U. Bracci," University of Rome "La Sapienza," 00101 Rome, Italy.

Future Directions in the Management of Benign Prostatic Hyperplasia

S. KHOURY

Clinique Urologique, L'Hôpital de la Pitié, Paris, France

Summary—A meeting of the International Consultation on Benign Prostatic Hyperplasia (BPH) in June 1991 provided an update on the management of BPH. It is recognised that the development of complications in what may be regarded as a relatively well tolerated disease may necessitate surgical intervention. Current treatment is directed towards circumventing or ameliorating the complications of BPH and perhaps to find minimally invasive or non-invasive alternatives to surgery that could eliminate this modality altogether. Anticipated changes in the management of BPH include establishment of an improved scoring system and response criteria; implementation of stenting techniques, physical modalities such as hyperthermia and laser therapy to replace transurethral resection of the prostate; development of more specific alpha blockers with fewer adverse effects; and administration of hormonal therapy, possibly as an eventual preventative of BPH.

The 1991 International Consultation on Benign Prostatic Hyperplasia (BPH), which took place in Paris, France, under the joint sponsorship of the World Health Organization and the major international and national societies of urology, provided an excellent opportunity to review current knowledge on the subject of BPH and to explore future trends in its management. Most of the information included in this report is drawn from the conclusions of the consultation participants.

Aetiology and Pathophysiology of BPH

Benign prostatic hyperplasia is essentially responsible for bladder neck obstruction, which accounts for the majority of the clinical symptoms of BPH. Classification of these symptoms places them into one of two categories:

- (1) Obstructive symptoms directly related to the enlarged prostate impeding urinary flow.
- (2) Irritative symptoms frequently triggered by the obstruction.

The type of bladder neck obstruction that is caused by BPH has two main mechanisms (Caine, 1986):

- (1) Mechanical or static mechanism, which depends on the volume, consistency and shape of the prostate.
- (2) Functional or dynamic mechanism, which is related to the tension exerted by the smooth muscle fibres present in the urethra, prostate and capsule.

These two factors play a variable role in obstruction, but the mechanical component largely predominates.

The three major aetiological factors of BPH are (1) the presence of functioning testes, (2) age and (3) race. From the fourth decade of life onward, both Asian and Caucasian men develop micronodules of BPH in their prostate. In native Asians, these microscopic nodules have a lesser tendency to enlarge and cause clinical symptoms and signs than they do in Caucasians. In Asians living in the United States, clinical BPH develops almost as frequently as it does in Caucasians. This epidemiological finding supposes the presence of not only genetic factors but also environmental and dietary factors, which would obviously be important to define.

The deterioration of the clinical symptoms and signs of BPH is signified by the development of complications. In fact, the complications of BPH may transform the disease from a relatively well

tolerated state to one that is incompatible with a normal life for the patient, often necessitating surgery.

Treatment

Although surgery remains the standard treatment for BPH, a number of less invasive techniques are currently being developed and are starting to occupy a place in the expanding range of treatments available. These techniques are summarised in Table 1.

The conclusions concerning the treatment alternatives for BPH as drawn at the International Consultation on BPH were presented by Smith *et al.* (1992) in an extensively documented report. New high-technology modalities were among the alternatives considered. Conclusions and future prospects regarding BPH treatment are succinctly presented and follow.

Table. BPH: Treatment Modalities

Functional

● Medical

Alpha blockers
Plant extracts

● Physical

Stents
Hyperthermia (<45°C)
Balloon dilatation

Mass reducing

● Surgery

● Physical

Thermotherapy (>45°C)
Cryosurgery
Laser
Focused external heat,
ultrasound, and
high-energy shock waves

● Medical

Hormone therapy

Alpha blockers

Alpha blockers are a therapeutic option for the symptomatic short-term (<6 months) treatment of BPH. At present, sufficient data are not available on the long-term (>6 months) effectiveness of these agents in BPH management (International Consensus Committee, 1992). The administration of alpha blockers in the treatment of BPH has tended to increase as clinicians have become more experi-

enced with this application of the drug. (Alpha blocker treatment is discussed in detail in the other chapters of this supplement.)

Plant extracts (Phytotherapy)

Some authors suggest that there may be a slight advantage to the use of plant extracts over placebo in the medical treatment of BPH (Fitzpatrick *et al.*, 1992). Their long-term benefit remains to be more accurately defined on a more scientific basis. These substances are widely used in some countries, particularly in Europe and Latin America.

Temporary stents and catheters

The intraurethral catheter and the Prostacath™ (Engineers and Doctors, Copenhagen, Denmark) and Urospiral™ (Porges, France) stents offer simple and relatively inexpensive methods of providing relief from retention of urine in patients who are too old or too ill to undergo a prostatectomy. They are simple to insert while the patient is under local anaesthesia and, if necessary, sedated. Apart from causing some irritation for the first few days, stents provide effective relief from retention of urine in two-thirds of the patients. In patients who require prolonged use, the stent should probably be changed at intervals to prevent encrustation (Nielsen *et al.*, 1990; Guazzoni *et al.*, 1991).

Permanent stents

Both the UroLume Wallstent (American Medical Systems, Minnetonka, USA) and the ASI stent (Advanced Surgical Interventions, Inc., San Clemente, USA) are suitable for patients in whom prostatectomy is a high-risk procedure. Either stent can be inserted with the patient under local anaesthesia and, if necessary, sedated. The complication rate is low if the stent is carefully placed, and the effect is permanent since the stent gradually becomes epithelialised with prostatic tissue. The diameter of the stent is such that subsequent cystoscopy is practicable without disturbing the stent. These stents are more expensive than temporary ones but are much less expensive than prostatectomy and more convenient for the patient than a permanent urethral catheter (Williams *et al.*, 1989; Williams, 1991).

Localised hyperthermia

In this technique the prostate is heated to a temperature between 42° and 45°C by the use of probes within the rectum or urethra. It is possible to relieve symptoms and often improve the flow

rate by 2–4 ml/s. Necrosis within the prostate does not occur, prostate size does not change, and TURP is likely to be required within 2 years for approximately a third of the patients (Baert *et al.*, 1990; Dreikorn *et al.*, 1990; Strohmaier, *et al.*, 1990).

Thermotherapy

With this form of treatment the prostate is heated to 45°–50°C with a urethral probe generating microwaves at 915 MHz. The urethra is protected by being kept cool while the prostatic tissue is damaged by the heat therapy; subsequent necrosis is seen. The probe works without the need to sedate the patient, it produces transient retention in 5–40% of patients, and it provides prolonged relief of symptoms with sustained increases in peak flow and reduced bladder pressure in 40% of patients.

Thermotherapy is not suitable for the patient with bladder neck stenosis, median lobe enlargement or a large prostate gland. However, for the patient whose prostate gland is 30–70 g in volume the technique is one that holds promise and is likely to be further refined (Devonec *et al.*, 1990a; 1990b; 1991).

Balloon dilatation

This technique (Klein, 1991; Long *et al.*, 1991) has been extensively evaluated and almost certainly depends on the anterior commissure of the prostate being split by the dilating balloon for its success; when this happens, the increase in flow rate is dramatic and the effect may be prolonged. Balloon dilatation is carried out with local anaesthesia and sedation, or with regional anaesthesia. Unfortunately, this technique is not suitable for patients with either a prominent middle lobe enlargement of the prostate or a large prostate gland. The balloons are expensive and in at least 50% of the patients the effect is short-lived, with symptoms and signs of obstruction returning within 1 year after dilatation.

Surgical treatment

Surgery is currently the standard treatment for BPH. It relieves symptoms and obstruction in about 85% of patients. During the past 2 decades, an important shift from open surgery to transurethral resection of the prostate (TURP) has been noted.

In BPH cases involving small-volume prostates, transurethral incision of the prostate (TUIP) gives excellent results with less morbidity than TURP. This technique is currently underused but will certainly gain preference among urologists in the future.

Cryotherapy

This form of treatment (Gonder *et al.*, 1964; Rigondet, 1976) has been evaluated for >20 years. While cryotherapy is effective in many patients, especially those in whom the prostate is not very large, the need for prolonged catheterisation in a significant number of patients makes it less attractive than many of the currently available alternatives, which are more convenient for the surgeon and the patient.

Laser therapy

The use of a side-firing laser or an open-fibre laser diffusing its energy within a balloon is still in an early stage of development. Both forms of treatment produce tissue destruction and thus far have demonstrated symptom relief in a canine model (Roth *et al.*, 1991). Laser therapy is likely to develop rapidly over the next 5 years and will probably challenge thermotherapy.

A clinical trial in which 8 centres are collaborating to compare transurethral laser incision of the prostate (TULIP) against conventional TURP is currently under way. The use of a laser at 20–40 watts at a pulse rate of 0.5–1.0 mm/s, with 6–9 passes for delivery of 5000–8000 joules, has been proposed. If the median lobe requires treatment, additional therapy is given at the same time.

The first patient series, which included 20 men, has been treated. Operating time averaged less than 30 min and included a laser application lasting 4 min. A catheter was left in overnight except in those patients who had retention of urine, in which case an indwelling suprapubic catheter was left in for 7 days. The average time in the hospital was 2.1 days. Of these 20 patients, 19 had $\geq 50\%$ improvement in their symptomatic score, or $\geq 50\%$ increase in the maximum flow rate. The improvement occurred gradually, over approximately 6 weeks, and has been maintained. As yet, no side effects have been seen. It seems that laser therapy is applicable to any prostate and is also simple to learn. However, since the temperatures (70°–100°C) produced by laser are higher than those produced by thermotherapy, regional or general anaesthesia is essential.

Laser therapy for the prostate is also being investigated by Newman *et al.* (unpublished data, 1991) at the M.D. Anderson Hospital and Tumor Institute in Houston, USA. This group hopes that the laser will prove practical for the destruction of all the glandular tissue within the prostate, which will render the technique potentially valuable as a treatment for localised prostatic cancer.

The possible uses of laser therapy are attracting much interest. Other investigators, including Watson of the Institute of Urology in England and Daikuzono of Japan, are experimenting with this modality by using a laser fibre within a balloon that dilates the prostate until a gauge of 60 French is reached and then diffuses the laser beam to achieve an "oven" effect. This technique has now been used by Watson in 10 patients and has produced a cavity in the prostatic urethra akin to that following TURP (unpublished data, 1991).

High-energy shock waves, focused external heat and focused ultrasound

These three alternative forms of BPH treatment are currently being developed. The first 2 methods require a lithotripter or similar device for their administration; the last—the focused ultrasound—is delivered transrectally. Each technique has been used in animal models and in a few patients (Foster *et al.*, 1991; Lobel *et al.*, 1991).

Hormonal treatment

It has been stated that a large number of men > 50 years of age exhibit some degree of prostatic enlargement due to BPH. The current belief is that a 40-year-old man has a 30% chance in his lifetime of undergoing a prostatectomy, generally TURP, to treat urinary flow obstruction. Given these odds, effective medical treatment of BPH would clearly appear to offer both economic and social benefits.

Androgen withdrawal induces the shrinkage of an enlarged prostate, so potential forms of BPH medical therapy have been directed toward blocking the action of androgens or suppressing their production within the prostatic tissue. These methods usually induce impotence and other secondary effects, so that their use in BPH is unacceptable.

5- α Reductase inhibitors. The inhibition of 5- α reductase and thereby the formation of dihydrotestosterone (DHT) from testosterone was considered a novel approach to BPH treatment and stimulated the search for 5- α reductase inhibitors (Gormley and Stoner, 1991). With the recent production of A-ring heterocyclic steroids and 4-azasteroids, which inhibit 5- α reductase, finasteride (MK-906) was developed and has recently been extensively tested in clinical trials.

Finasteride decreases the DHT concentration in prostatic tissue and its administration results in a reduction in the plasma DHT level while the testosterone level is maintained. The effect of testosterone on libido is therefore not affected and

its anabolic action on muscle tissue is retained. Finasteride will also maintain the normal androgenic features promoted by testosterone in a manner similar to male children with inherited 5- α reductase deficiency, who develop a normal libido at puberty as characterised by a deep voice, male sexual features and musculature but have a small prostate and scanty beard growth.

In early clinical studies, 50 mg finasteride administered daily for 7 days decreased intraprostatic DHT by 92% but increased the concentration of testosterone from 0.23 ± 0.18 ng/g to 1.9 ng/g. When administered at a dose of 5 mg daily for 6 months, finasteride decreased the plasma DHT concentration by 80% to "castrate" levels, shrank prostatic volume by 28%, and increased the urine flow rate up to 3 ml/s without adverse clinical effects.

Aromatase inhibitors and antioestrogens. The aromatase enzyme system is responsible for the conversion of androgens to oestrogens. It is particularly active in the ovary and placenta but is also present in the testes and such extragonadal sources as adipose tissue and muscle. The possibility that oestrogens may be implicated in the pathogenesis of BPH has consistently provoked interest in the potential value of aromatase inhibitors as well as antioestrogens in the clinical management of the disease.

Experimental studies in dogs and monkeys have indicated that prostatic stromal proliferation, which is induced by the administration of androstenedione, can be antagonised by simultaneous administration of aromatase inhibitors such as 4-hydroxyandrostenedione and 1-methylandrosta-1,4-diene-3,17-dione (M-AD). In preliminary studies of patients with BPH, M-AD significantly decreased the plasma concentrations of oestrone and oestradiol (Habenicht and El Etreby, 1987). Nonetheless, it also would seem logical to consider an effective means of blocking the biological effects of oestrogen at the target cells by use of antioestrogen therapy. An earlier study using the antioestrogen tamoxifen administered for 4 weeks before prostatectomy at a dosage of 80 mg/d promoted stromal proliferation and was reported to be unsuccessful. It is not surprising that stromal hyperplasia was a consequence of this treatment, because a daily dose of tamoxifen amounting to only 20 mg has been found to be efficacious in the treatment of premenopausal women with breast cancer and because tamoxifen is known to act like a weak oestrogen. Therefore, it would seem more

logical to use lower doses of tamoxifen, possibly in association with a 5- α reductase inhibitor or a low-dose antiandrogen, for the treatment of BPH. It will soon be possible to consider the new ICI 183,720, which is a complete oestrogen antagonist with no oestrogenic properties, for the management of BPH.

Future Prospects in the Treatment of BPH

The field of medicine is marked by a number of archetypal constants:

- (1) Medical progress in surgical diseases involves the use of less invasive surgical methods until surgical treatment is finally replaced by medical treatment.
- (2) Whenever a drug competes with a surgical procedure, the drug eventually gains preference. Patients have a natural aversion to surgery, however minor, and often prefer even a drug with unpleasant side effects to an operation with no or minimal sequelae.

The Figure illustrates the comparative value of the various treatment modalities for BPH over the next 5 years and by the end of the century. There are no quantitative data, which would be impossible to present—simply impressions principally based on current knowledge of the potential uses of new BPH treatment modalities and on analogies of what has evolved in the management of other diseases, such as renal calculi and duodenal ulcers.

Future treatment of BPH will inevitably lean

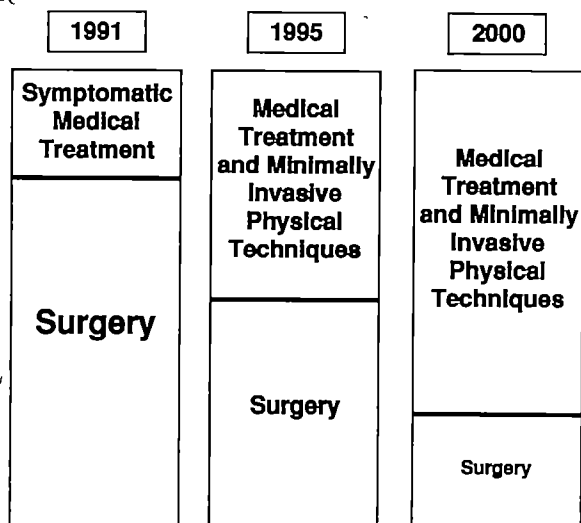


Fig. Comparative value of the various treatment modalities for BPH over the next 5 years and by the end of the century.

toward replacement of surgical treatment by new, less aggressive methods that will ensure the same reduction in prostatic mass. In turn, these methods will be subsequently replaced by drug treatment only. In the meantime, symptomatic medical treatment will remain important as sole therapy for early-stage disease and as adjuvant therapy for more advanced cases.

Over the next 5 years

The therapeutic approach to BPH over the next 5 years will be marked by several new elements:

- (1) A better symptom scoring system and better response criteria will be developed.
- (2) Physical treatment modalities will be further developed. In view of their minimally invasive nature, which does not necessitate the induction of anaesthesia, they will inevitably replace TURP in a number of years, especially for uncomplicated cases in which surgery is indicated to lessen discomfort and for patients with a relatively short life expectancy or at high risk. The extensive development of these techniques will be the outstanding event in the field of BPH management over the next 5 years.
- (3) Alpha blockers will confirm their role as the most effective symptomatic medical treatment.
- (4) Hormone therapy will enter the field. Because several weeks are needed to achieve an effect that will only be partial in a number of cases, these agents will probably be combined with alpha blockers, at least during the initial months of treatment.
- (5) In the field of surgery, TURP will continue to gain ground on open surgery as a result of constant improvement in surgical devices, the growing experience acquired by urologists and better training methods. The indications for bladder neck incision will increase, given that a large number of BPH cases currently treated by surgery involve prostates weighing approximately 25 g.

By the end of the century

New, more specific alpha blockers with fewer adverse effects will be developed. Hormonal treatment will become more complex, probably combining 5- α reductase inhibitors with the new, pure antioestrogens currently under investigation. The possible discovery of a specific growth factor in the prostate could completely change BPH treatment perspectives. A preventive approach will also develop.

The greatest technical progress will concern the performance of the various physical methods. Lasers will certainly have a place in reducing the prostatic mass. By the end of the century, these techniques will have almost completely replaced surgery as it is known today in the great majority of cases.

References

- Baert, L., Ameye, F., Willemen, P. *et al.* (1990). Transurethral microwave hyperthermia for benign prostatic hyperplasia: preliminary clinical and pathological results. *J. Urol.*, **144**, 1383–1387.
- Calne, M. (1986). The present role of alpha-adrenergic blockers in the treatment of benign prostatic hypertrophy. *J. Urol.*, **136**, 1–4.
- Devonoc, M., Berger, N. and Perrin, P. (1991). Transurethral microwave heating of the prostate—from hyperthermia to thermotherapy. *J. Endourol.*, **5**, 129–136.
- Devonoc, M., Cathaud, H., Carter, S. *et al.* (1990a). Histological and clinical effects of transurethral microwave therapy in patients with benign prostatic hypertrophy. Presented at the XMII Krongres des Deutschen Gesellschaft fur Urologie; September 26–29; Hamburg, Germany.
- Devonoc, M., Cathaud, M., Carter, J. *et al.* (1990b). Transurethral microwave therapy (TUMT) in patients with benign prostatic hypertrophy Presented at the 8th World Congress on Endourology and ERSWL; August 29–September 2; Washington, D.C. Abstract.
- Dreikorn, K., Richter, R. and Schonhofer, P. S. (1990). Konservativ nicht-hormonelle Behandlung der benignen Prostata Hyperplasie. *Urologe*, **29** (Suppl A), 8.
- Fitzpatrick, J. M., Dreikorn, K., Khoury, S. *et al.* (1992). The medical management of BPH with agents other than hormones and α blockers. In: *Proceedings of the International Consultation on Benign Prostatic Hyperplasia (BPH)*; June 26–27, 1991; Paris; ed. Cockett A. T. K., Aso, Y., Chatelain, C. *et al.* Pp. 193–199. Paris: SCI.
- Foster, R. S., Bihle, R., Sanghvi, N. T. *et al.* (1991). Noninvasive ultrasound produced volume lesion in prostate. *J. Urol.*, **145**, 396A. Abstract No. 735.
- Gonder, M. J., Soanes, W. A. and Smith, V. (1964). Experimental prostate cryosurgery. *Invest. Urol.*, **1**, 610–619.
- Gormley, G. J. and Stoner, E. (1991). The role of 5 α -reductase inhibitors in the treatment of benign prostatic hyperplasia. In: *Problems in Urology*, ed. Lepor, H. and Paulson, D. F. Vol. 5, No. 3 Pp 436–440. Lippincott: Philadelphia.
- Guazzoni, G., Montorsi, F., Colombo, R. *et al.* (1991). Long term experience with the prostatic spiral for urinary retention due to benign prostatic hyperplasia. *Scand. J. Urol. Nephrol.*, **25**, 21–24.
- Habenicht, U.-F. and El Etreby, M. F. (1987). Synergic inhibitory effects of the aromatase inhibitor 1-methyl-androsta-1,4-diene-3,17-dione and the antiandrogen cyproterone acetate on androstenedione-induced hyperplastic effects in the prostates of castrated dogs. *Prostate*, **11**, 133–143.
- International Consensus Committee. (1992). 4 BPH treatment recommendations. In: *Proceedings of the International Consultation on Benign Prostatic Hyperplasia (BPH)*; June 26–27, 1991; Paris; ed. Cockett, A. T. K., Aso, Y., Chatelain, C. *et al.* Pp. 287–288. Paris: SCI.
- Klela, L. A. (1991). 2 year follow-up of balloon dilatation of the prostate and an algorithm for future patient selection. *J. Endourol.*, **5**, 109–112.
- Lobel, B., Gille, F., Cipolla, B. *et al.* (1991). High energy shock waves (HESW) for the treatment of benign prostatic hypertrophy (BPH). *J. Urol.*, **145**, 396A. Abstract No. 735.
- Long, S. R., Clayman, R. V., Dierks, S. M. *et al.* (1991). Balloon incision of the prostate: preliminary evaluation of a minimal invasive technique. *J. Endourol.*, **5**, 117–122.
- Nielsen, K. K., Klarskov, P., Nordling, J. *et al.* (1990). The intraprostatic spiral: new treatment for urinary retention. *Br. J. Urol.*, **65**, 500–503.
- Rigondet, G. (1976). Etude comparee de 325 cas de cryochirurgie utilisant comme refrigerant le protoxyde d'azote et l'azote liquide. *Ann. Urol.*, **10**, 159–162.
- Roth, R. A., Babayan, R. and Aretz, H. T. (1991). TULIP—transurethral ultrasound-guided laser-induced prostatectomy. *J. Urol.*, **145**, 390A. Abstract No. 712.
- Smith, Ph., Chaussy, C., Comort, P. *et al.* (1992). Report of the committee on other non medical treatment. In: *Proceedings of the International Consultation on Benign Prostatic Hyperplasia (BPH)*; June 26–27, 1991; Paris; ed. Cockett, A. T. K., Aso, Y., Chatelain, C. *et al.* Pp. 223–257. Paris: SCI.
- Strohmaier, W. L., Bichler, K. H., Flüchter, S. H. *et al.* (1990). Local microwave hyperthermia of benign prostatic hyperplasia. *J. Urol.*, **144**, 913–917.
- Williams, G. (1991). Early experience of the use of permanently implanted prostatic stents for the treatment of bladder outflow obstruction. *World J. Urol.*, **9**, 26–28.
- Williams, G., Jager, R., McLoughlin, J. *et al.* (1989). Use of stents for treating obstruction of urinary outflow in patients unfit for surgery. *Br. Med. J.*, **298**, 1429.

The Author

S. Khoury, MD, Professor of Urology, Clinique Urologique, L'Hôpital de la Pitié, Paris, France.

Requests for reprints to: S. Khoury, Clinique Urologique, L'Hôpital de la Pitié, Cedex 13, 75634 Paris, France.

Challenges in the Management of Prostate Cancer

E. D. CRAWFORD

Division of Urology, University of Colorado Health Sciences Center, Denver, Colorado, USA

Summary—An estimated 32,000 American men will die of prostate cancer this year. Local prostate cancer may be successfully treated by radical prostatectomy or radiotherapy. Advanced cases may necessitate the use of hormonal ablation with bilateral orchiectomy, an approach that is regarded as the gold standard of therapy but not always the preferred treatment of patients. Oestrogen therapy is an alternative but is associated with side effects, such as hot flushes and gynaecomastia, which frequently lead to treatment cessation. Luteinising hormone-releasing hormone (LHRH) analogues work by initially producing a surge of androgen, followed by a down-regulation in hormone production to effect a medical castration. Various groups have studied the effects of androgen blockade administered as monotherapy and as combination therapy (LHRH analogue plus anti-androgen). The National Cancer Institute intergroup protocol 0036, which is the largest co-operative study to date of patients with advanced prostatic cancer, showed that combination therapy with leuprolide and flutamide offered greater benefit in both time to disease progression and median survival while circumventing tumour flare and its associated symptoms. Thus, combination therapy for total androgen ablation may become the new treatment standard for advanced prostatic cancer, pending further studies in the efficacy and cost-effectiveness of all available treatments.

The National Cancer Institute estimates that 132,000 new cases of prostate cancer will be diagnosed this year in the United States alone (Boring *et al.*, 1992). Furthermore, an estimated 34,000 American men will die of prostate cancer. Although radical prostatectomy or radiotherapy is frequently successful in treating carcinoma that is confined to the prostate, only 60% of all patients with prostatic cancer initially present with carcinoma that is still localised (Boring *et al.*, 1992). Treatment beyond radiotherapy or localised surgery is therefore required for a substantial number of patients with advanced prostatic cancer.

Overview of Treatment Methods

As early as 1941, Huggins and Hodges demonstrated that progression of prostatic cancer could be slowed by hormonal intervention. Because prostatic cancer cell growth generally correlates with androgen levels, Huggins and Hodges reduced patient androgen levels by injection of oestrogens

or by bilateral orchiectomy. Huggins was awarded a Nobel Prize for this work in 1953; bilateral orchiectomy has since become the gold standard treatment for this condition.

While surgical castration would be accepted by most patients, it may not be their treatment preference, all things being equal. Cassileth *et al.* (1989) reported in their multicentre study in the United States that patients offered a choice between orchiectomy or current hormonal therapy chose the non-surgical modality more than 78% of the time.

In reality, all things are not equal between the various treatments. Bilateral orchiectomy has few associated complications, can be performed easily under local anaesthesia if necessary, and is relatively low in cost. Side effects include impotence (which is common to most current therapies) and hot flushes. The effectiveness of this therapy is based on the fact that the testes produce approximately 95% of the circulating androgens.

Historically, oestrogen therapy as a non-invasive alternative to orchiectomy has also been shown effectively to reduce testosterone to castrate levels

within 7–21 days. This reduction occurs as oestrogens suppress the secretion from the hypothalamus of luteinising hormone-releasing hormone (LHRH). Without this suppression, LHRH would act on the pituitary to cause secretion of LH. LH would then stimulate the testes to produce testosterone.

However, although oestrogen has been shown to effectively reduce the level of circulating androgens, its effectiveness must be weighed against any associated cardiovascular risk. A study by Henriksson and Edhag (1986) found that 25% of patients experienced a serious cardiovascular event necessitating hospitalisation within a mean of 5 months after initiation of oestrogen therapy. In contrast, no such events were associated with orchiectomy. Recent work in titrating the maintenance dose of oestrogen to a more tolerable level has revealed, for example, that diethylstilboestrol (DES) administered daily as a 3 mg dose was safer than the traditional 5 mg dose, while still reasonably effective in reducing the serum testosterone to anorchid levels (Prout *et al.*, 1976; Resnick, 1984; Stege *et al.*, 1989). Other side effects of this treatment include nausea and vomiting, gynaecomastia, breast tenderness and hot flushes.

Other works examining the role of oestrogen in male development have shown that oestrogens may actually act in synergy with androgens or possibly even act alone to stimulate prostate cell growth (Mawhinney and Neubauer, 1979; Thompson *et al.*, 1979). Additionally, tissue concentrations of oestrogens have been found to be higher in prostates with neoplasms than in those with benign prostatic hyperplasia (Ghanadian and Puah, 1981). These findings may indicate that oestrogen therapy for prostatic cancer may need to be re-examined.

A newer hormonal method of reducing the level of testosterone uses LHRH analogues, which have been shown to be approximately 100 times more potent than natural LHRH. Long-term use of these potent hormones eventually desensitises the pituitary to hormonal stimulation, paradoxically but effectively down-regulating the production of testicular testosterone. Numerous studies have shown therapy with LHRH analogues such as leuprolide (Lupron, TAP Pharmaceuticals, Bannockburn, USA) or goserelin (Zoladex, ICI Pharma, Wilmington, USA) to be as effective as orchiectomy or oestrogen therapy in reducing testosterone levels (Warner *et al.*, 1983; Sharifi, 1985; Ahmann *et al.*, 1987; Murphy *et al.*, 1987; Seely, 1987; Beacock, 1988; Borgmann *et al.*, 1988; Debruyne *et al.*, 1988; Kotake *et al.*, 1988; Soloway *et al.*, 1988; Waxman,

1988; Peeling, 1989). Surgery is avoided, and many of the serious side effects of oestrogen therapy, including cardiovascular effects, are significantly reduced.

A randomised, multicentre study compared the effects of leuprolide versus DES and found no significant difference between treatment groups in time to disease progression (Leuprolide Study Group, 1984). However, a significantly higher incidence of side effects such as peripheral oedema, nausea and vomiting, gynaecomastia and hot flushes was experienced by the oestrogen group. This group also had a greater trend toward deep venous thrombosis, phlebitis and pulmonary embolus. Mean survival time was not established at the time of publication of the study. A similar study with goserelin also showed minimal side effects, with efficacy equivalent to that of oestrogen therapy.

Other studies indicate that LHRH may decrease testosterone through more than one route. Although the primary site of action for LHRH is the pituitary gland, some evidence indicates that secondary LHRH receptors in the testes and the prostate may also help to decrease testosterone levels.

Aetiology and Management of Metastatic Disease

Although there have been significant advances in the management of prostate cancer, patient mortality due to metastatic disease is still high 5 years after diagnosis. Two theories have been advanced to explain the metastasis of prostate cancer, which develops despite the low circulating levels of testosterone. Both theories are based on the idea that tumour cells are heterogenous in the amount of androgen that they require for growth.

The first theory states that surgical or chemical castration inhibits "androgen-dependent" cells, or cells that cannot grow without normal levels of testosterone. However, this theory postulates that some cells in the tumour population will, by chance, require a very low level of androgen for growth; such cells are considered to be "androgen-sensitive". Since traditional treatments for prostatic cancer inhibit production of androgens by the testes without inhibiting hormonal production by the adrenal gland, androgen-sensitive tumour cells might be able to thrive on the low levels of androgens produced by this alternate pathway.

Androstenedione, dihydroepiandrosterone, and the sulphate derivative of dihydroepiandrosterone are the primary adrenal androgens (Labrie *et al.*, 1983). Although these androgens are only 5–10% as potent as testosterone, they normally compose

approximately 15–20% of the total dihydrotestosterone (DHT) present in the prostate (Harper *et al.*, 1974). In fact, these hormones may be metabolised to testosterone or to DHT either in the plasma or in the prostate itself. Labrie *et al.* (1987c) reported that after traditional treatment such as orchiectomy or LHRH agonists, as much as 50% of the intraprostatic DHT remained. Furthermore, these adrenal androgens have been shown to aid in the growth of prostatic cells in animal models. Research by Tullner (1963), whose studies involved castrated rats, showed that supplemental adrenocorticotrophic hormone (ACTH) promoted growth of the ventral prostate, although no such prostatic growth occurred in adrenalectomised animals.

If prostatic cancer progresses as a result of the postulated androgen-sensitive cells, then elimination of the adrenal androgens may slow or halt disease progression. As early as 1945, Huggins and Scott attempted such treatment by performing bilateral adrenalectomy in 4 patients. However, the procedure did not improve patient mortality in this group, probably because of inadequate adrenal hormone replacement therapy at that time.

Miller and Hinman first attempted "medical adrenalectomy" through the administration of cortisone treatment in 1954 but the idea of total androgen ablation with the use of anti-androgens was re-popularised by Labrie *et al.* in the 1980s (Labrie *et al.*, 1983; 1985; 1986b; 1987a; 1987b). A series of studies in the early 1980s showed excellent treatment results, but there were no placebo-matched controls (Labrie *et al.*, 1982; Belanger *et al.*, 1984; Labrie and Veilleux, 1986; Labrie *et al.*, 1986a; Labrie *et al.*, 1987b).

Opponents of combined androgen ablation propose an alternate hypothesis which states that some prostatic cancer cells are not androgen-sensitive but rather androgen-independent. These cells are believed to require essentially no androgen for growth. In experiments with an androgen-sensitive rat model displaying a tumour classified by the Dunning system, it was found that lowering the testosterone level below 0.25 ng/ml gave no further benefit in tumour growth retardation (Isaacs, 1982; Ellis and Isaacs, 1985). In other words, cells that could proliferate with a minimal level of testosterone also seemed to be capable of proliferating without the presence of testosterone. Furthermore, rat survival rates were no better with combined orchiectomy and anti-androgens than with orchiectomy alone.

Various groups trying to reproduce this experiment or similar ones saw different results. Some

found that combination therapy offered no benefit beyond that of monotherapy (Fox and Hammonds, 1980; Brisset *et al.*, 1987; Robinson, 1987); other groups found that combination therapy was advantageous (Trachtenberg *et al.*, 1983; Crawford *et al.*, 1987, 1990; Debruyne *et al.*, 1987; Murray and Pitt, 1987; Navratil, 1987; Smith, 1987).

The NCI study

The National Cancer Institute (NCI) investigated the disparity of opinion regarding combination therapy by setting up the largest co-operative study to date of patients with advanced prostate cancer. Referred to as protocol 0036, it randomised half of the patients to a treatment of leuprolide plus flutamide, a synthetic non-steroidal anti-androgen, and the other half to leuprolide plus placebo. Leuprolide was administered orally on a daily basis, as the depot formulation was not available when the study was initiated. A total of 603 patients were evaluable. The results of this study were published in 1989 (Crawford *et al.*, 1989).

Fig. 1 shows the time from study entry to disease progression. Median time to prostatic cancer progression was 3.1 months longer in the group receiving flutamide. Median survival time was 5.8 months longer in this same group (Fig. 2). The results showed obvious benefit with total androgen ablation.

Two findings were significant but unexpected in the NCI study. The first finding was the strong correlation of good performance scores upon initial examination, with increased benefit seen after the administration of flutamide. For those patients with poor initial performance scores, there was no benefit to anti-androgen therapy. In fact, those patients given placebo actually had a median time

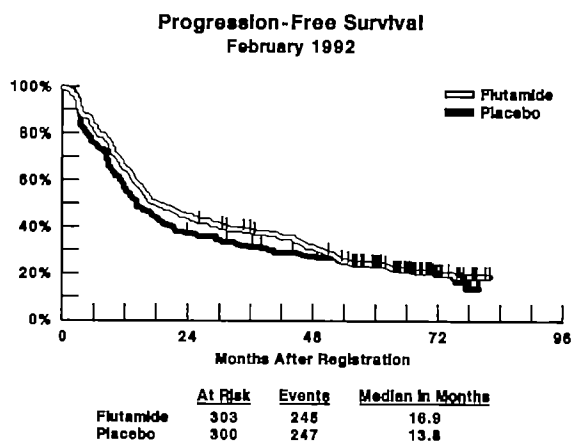


Fig. 1 Time from study entry to progression of prostatic cancer.

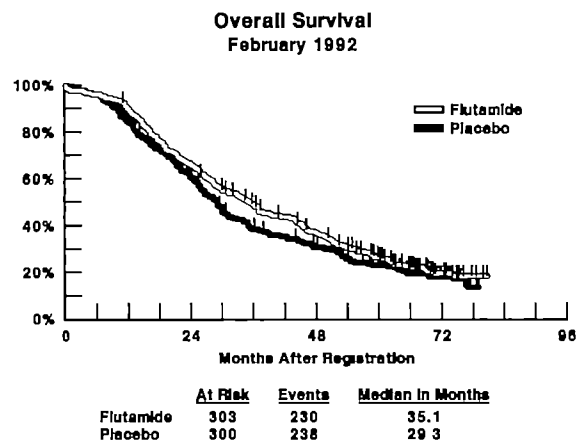


Fig. 2 Survival time for patients with prostatic cancer.

to disease progression that was 0.5 months longer than that of patients given flutamide, as well as median survival time that was 2.6 months longer. Among those patients with good initial performance scores and severe disease, however, leuprolide plus flutamide added 3.2 months to the median time to disease progression and 6.9 months to the median survival time. For those patients with good performance scores and minimal disease, the addition of the anti-androgen added 39.2 months to the time to disease progression, making the median time to progression 58.3 months (Fig. 3). The median survival time for this group was 61.0 months, an increase of 19.5 months over that of the placebo group (Fig. 4).

The second surprising finding was that race also seemed to be associated with survival. The median survival time for blacks with prostate cancer was

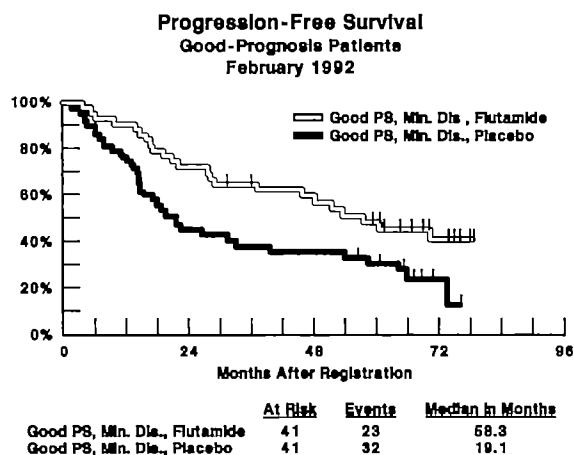


Fig. 3 Progression of prostatic cancer in relation to initial performance scores (PS) and extent of disease (min dis., minimal disease).

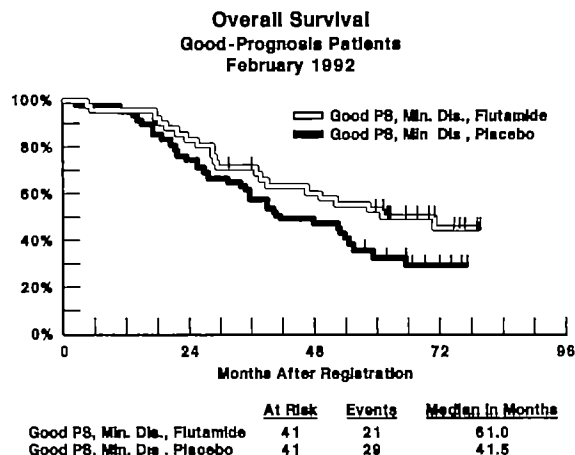


Fig. 4 Survival time in relation to initial performance scores (PS) and extent of disease (min. dis., minimal disease)

6.1 months less than that for non-blacks. Fig. 5 shows the survival curve by race. The proportion of severe disease and poor initial performance status seen in blacks was similar to the proportion seen in non-blacks, yet overall response to treatment was worse among blacks. This finding cannot be explained.

In general, the NCI study showed that combined androgen blockade offers benefit both in time to disease progression and in median survival time for patients with severe prostatic cancer. Those who had good performance scores and those with less severe disease were more likely to benefit from treatment. Assessment of disease severity was based on the bone scan results. There was also a correlation between the severe disease category and factors such as anaemia, bone pain, anorexia, weight loss and use of analgesics.

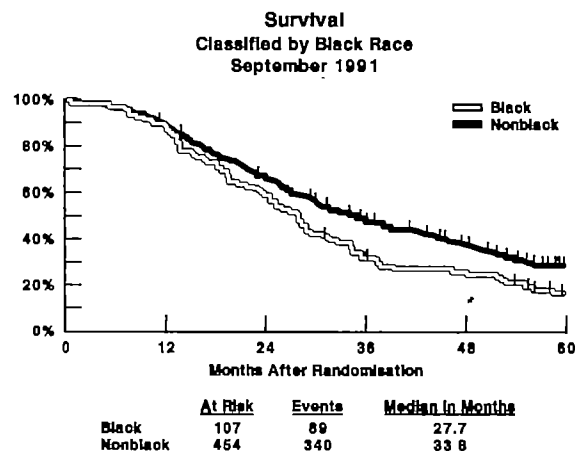


Fig. 5 Survival time in black and non-black patients with prostatic cancer.

Another advantage of combined androgen blockade therapy is the prevention of the tumour flare that is sometimes associated with LHRH agonists administered alone. Although long-term doses of these hormones eventually desensitise the pituitary, initial doses merely stimulate overproduction of androgen, which can exacerbate hormone-dependent disease. LHRH agonists cause testosterone levels to peak approximately 74 h after initiation of therapy and then to gradually decrease to castrate levels. Although there is no evidence that tumour flare affects the survival rate, combined androgen blockade can alleviate symptoms associated with the phenomenon. These include increased bone pain, increased outlet obstruction, increased serum creatinine concentrations and spinal cord compression.

Various other drugs can block and/or alter adrenal androgens. These drugs include anadron, cyproterone acetate, ketoconazole, spironolactone, glucocorticoids and aminoglutethimide. Non-steroidal anti-androgens such as flutamide and anadron exert their effect at the target androgen receptor, regardless of serum levels of testosterone. Thus, they have the potential to inhibit both testicular and adrenal androgens. However, these agents have not been studied as extensively as monotherapy.

LHRH therapy with anti-androgens is a controversial treatment for advanced or metastatic prostatic cancer. Previous studies have shown leuprolide and goserelin to be equivalent to bilateral orchiectomy or oestrogen therapy, with fewer side effects than oestrogen therapy. The NCI study confirms the findings of Labrie and numerous other researchers (Trachtenberg *et al.*, 1983; Crawford *et al.*, 1987; Debruyne *et al.*, 1987; Murray and Pitt, 1987; Navratil, 1987; Smith, 1987), in which combination androgen blockade was found to be more beneficial than monotherapy in terms of median time to disease progression and median survival time.

Other studies are needed to address the difference in treatment efficacy between subsets of patients, as well as the cost-effectiveness of the various therapeutic modalities. In the meantime, total androgen ablation may attain status as the new standard of treatment for advanced prostatic cancer.

References

- Abmann, F. R., Citrin, D. L., deHaan, H. A. *et al.* (1987). Zoladex: a sustained-release, monthly luteinizing hormone-releasing hormone analogue for the treatment of advanced prostate cancer. *J. Clin. Oncol.*, **5**, 912-917.
- Beacock, C. J. M. (1988). Long-term results of treating advanced prostatic cancer with the LH-RH analogue Zoladex. *Am. J. Clin. Oncol.*, **11**(Suppl 2), S115-S116.
- Belanger, A., DuPont, A. and Labrie, F. (1984). Inhibition of basal and adrenocorticotropin-stimulated plasma levels of adrenal androgens after treatment with an antiandrogen in castrated patients with prostatic cancer. *J. Endocrinol. Metab.*, **59**, 422-426.
- Borgmana, V., Al-Abadi, H. and Nagel, R. (1988). Treatment of locally advanced prostatic carcinoma with LHRH analogues: cytological, DNA-cytophotometrical, and clinical results. *Am. J. Clin. Oncol.*, **11**(Suppl 1), S19-S28.
- Boring, C. C., Squires, T. S. and Tong, T. (1992). Cancer statistics, 1991. *Ca-A Cancer J Clinicians*, **41**, 19-37.
- Briset, J.-M., Boccon-Gibod, L., Botto, H. *et al.* (1987). Anadron (RU 23908) associated to surgical castration in previously untreated stage D prostate cancer: a multicenter comparative study of two doses of the drug and of a placebo. In *Prostate Cancer, Part A: Research, Endocrine Treatment, and Histopathology*, ed. Murphy, G. P., Küss, R., Khoury, S. *et al.* Pp. 411-422. New York: Alan R. Liss.
- Cassileth, B. R., Soloway, M. S., Vogelzang, N. J. *et al.* (1989). Patients' choice of treatment in stage D prostate cancer. *Urology*, **33**(Suppl 5), 57-62.
- Crawford, E. D., Ahmann, F. R., Davis, M. A. *et al.* (1987). Aminoglutethimide in metastatic adenocarcinoma of the prostate. In *Prostate Cancer, Part A: Research, Endocrine Treatment, and Histopathology*, ed. Murphy, G. P., Küss, R., Khoury, S. *et al.* Pp. 283-289. New York: Alan R. Liss.
- Crawford, E. D., Eisenberger, M. A., McLeod, D. G. *et al.* (1989). A controlled trial of leuprolide with and without flutamide in prostatic carcinoma. *N. Engl. J. Med.*, **321**, 419-424.
- Crawford, E. D., Goodman, P. and Blumenstein, B. (1990). Combined androgen blockade: leuprolide and flutamide versus leuprolide and placebo. *Semin Urol.*, **8**, 154-158.
- Debruyne, F. M. J., Denis, L., Lunglmayer, G. *et al.* (1988). Long-term therapy with a depot luteinizing hormone-releasing hormone analogue (Zoladex) in patients with advanced prostatic carcinoma. *J. Urol.*, **140**, 775-777.
- Debruyne, F. M. J., Witjes, F. A. and the Dutch South-Eastern Urological Cooperative Group. (1987). Ketoconazole high dose (H.D.) in the management of hormonally pretreated patients with progressive metastatic prostate cancer. In *Prostate Cancer, Part A: Research, Endocrine Treatment, and Histopathology*, ed. Murphy, G. P., Küss, R., Khoury, S. *et al.* Pp. 301-313. New York: Alan R. Liss.
- Ellis, W. and Isaacs, J. T. (1985). Effectiveness of complete versus partial androgen withdrawal therapy for the treatment of prostatic cancer as studied in the Dunning R-3327 system of rat prostatic adenocarcinomas. *Cancer Res.*, **45**, 6041-6050.
- Fox, M. and Hammonds, J. C. (1980). Palliative effect of cyproterone acetate in carcinoma of the prostate with widespread metastatic bone disease. *Br. J. Urol.*, **52**, 402.
- Ghanadian, R. and Pash, C. M. (1981). Relationships between oestradiol-17 β , testosterone, dihydrotestosterone and 5 α -androstane-3 α , 17 β -diol in human benign hypertrophy and carcinoma of the prostate. *J. Endocrinol.*, **88**, 255-262.
- Harper, M. E., Pike, A., Peeling, W. B. *et al.* (1974). Steroids of adrenal origin metabolized by human prostate tissue both in vivo and in vitro. *J. Endocrinol.*, **60**, 117-125.
- Henriksson, P. and Edhag, O. (1986). Orchiectomy versus oestrogen for prostatic cancer: cardiovascular effects. *Br. Med. J.*, **293**, 413-415.
- Huggins, C. and Hodges, C. V. (1941). Studies on prostatic cancer I. The effect of castration, of estrogen, and of androgen

- injection on serum phosphatases in metastatic carcinoma of the prostate. *Cancer Res.*, **1**, 293-297.
- Huggins, C. and Scott, W. W. (1945). Bilateral adrenalectomy in prostatic cancer. *Ann. Surg.*, **122**, 1031-1041.
- Isaacs, J. T. (1982). Hormonally responsive versus unresponsive progression of prostatic cancer to antiandrogen therapy as studied with the Dunning R-3327-AT and -G rat adenocarcinomas. *Cancer Res.*, **42**, 5010-5014.
- Kotake, T., Usami, M., Sonoda, T. *et al.* (1988). LH-RH agonist, Zoladex (goserelin), depot formulation in the treatment of prostatic cancer: randomized dose-finding trial in Japan. *Am. J. Clin. Oncol.*, **11**(Suppl 2), S108-S111.
- Labrie, F., Dupont, A., Belanger, A. *et al.* (1985). Combination therapy with flutamide and castration (LHRH agonist or orchiectomy) in advanced prostate cancer: a marked improvement in response and survival. *J. Steroid Biochem. Mol. Biol.*, **23**, 833-841.
- Labrie, F., Dupont, A., Belanger, A. *et al.* (1987a). Flutamide eliminates the risk of disease flare in prostatic cancer patients treated with a luteinizing hormone-releasing hormone agonist. *J. Urol.*, **138**, 804-806.
- Labrie, F., Dupont, A., Belanger, A. *et al.* (1983). New approach in the treatment of prostate cancer: complete instead of partial withdrawal of androgens. *Prostate*, **4**, 579-594.
- Labrie, F., Dupont, A., Belanger, A. *et al.* (1982). New hormonal therapy in prostatic carcinoma: combined treatment with an LHRH agonist and an antiandrogen. *Clin. Invest. Med.*, **5**, 267-275.
- Labrie, F., Dupont, A., Belanger, A. *et al.* (1986a). Treatment of prostate cancer with gonadotropin-releasing hormone agonists. *Endocr. Rev.*, **7**, 67-74.
- Labrie, F., Dupont, A., Giguere, M. *et al.* (1986b). Advantages of the combination therapy in previously untreated and treated patients with advanced prostate cancer. *J. Steroid Biochem. Mol. Biol.*, **25**, 877-883.
- Labrie, F., Dupont, A., Giguere, M. *et al.* (1987b). Combination therapy with flutamide and castration (orchiectomy or LHRH agonist): the minimal endocrine therapy in both untreated and previously treated patients. *J. Steroid Biochem. Mol. Biol.*, **27**, 525-532.
- Labrie, F., Luthy, I., Veilleux, R. *et al.* (1987c). New concepts on the androgen sensitivity of prostate cancer. In *Prostate Cancer, Part A: Research, Endocrine Treatment, and Histopathology*, ed. Murphy, G. P., Küss, R., Khoury, S. *et al.* Pp 145-172. New York: Alan R. Liss.
- Labrie, F. and Veilleux, R. (1986). A wide range of sensitivities to androgens develops in cloned Shionogi mouse mammary tumor cells. *Prostate*, **8**, 293-300.
- Leuprolide Study Group. (1984). Leuprolide versus diethylstilbestrol for metastatic prostate cancer. *N. Engl. J. Med.*, **311**, 1281-1286.
- Mawhinney, M. G. and Neubauer, B. L. (1979). Actions of estrogen in the male. *Invest. Urol.*, **16**, 409-420.
- Miller, G. M. and Hinman, F., Jr. (1954). Cortisone treatment in advanced carcinoma of the prostate. *J. Urol.*, **72**, 485-495.
- Murphy, G. P., Greco, J. M., Chin, J. L. *et al.* (1987). Zoladex (ICI 118,630): clinical trial of new luteinizing hormone-releasing hormone analog in metastatic prostatic carcinoma. *Urology*, **29**, 185-190.
- Murray, R. and Pitt, P. (1987). Aminoglutethimide in the treatment of advanced prostatic cancer. In *Prostate Cancer, Part A: Research, Endocrine Treatment, and Histopathology*, ed. Murphy, G. P., Küss, R., Khoury, S. *et al.* Pp. 275-282. New York: Alan R. Liss.
- Navratil, H. (1987). Double-blind study of anadron versus placebo in stage D₂ prostate cancer patients receiving busferlin: results on 49 cases from a multicentre study. In *Prostate Cancer, Part A: Research, Endocrine Treatment, and Histopathology*, ed. Murphy, G. P., Küss, R., Khoury, S. *et al.* Pp. 401-410. New York: Alan R. Liss.
- Peeling, W. B. (1989). Phase III studies to compare goserelin (Zoladex) with orchiectomy and with diethylstilbestrol in treatment of prostatic carcinoma. *Urology*, **33**(Suppl), 45-52.
- Prout, G. E., Jr., Kilman, B., Daly, J. J. *et al.* (1976). Endocrine changes after diethylstilbestrol therapy: effect on prostatic neoplasm and pituitary-gonadal axis. *Urology*, **7**, 148-155.
- Resnick, M. I. (1984). Hormonal therapy in prostatic carcinoma. *Urology*, **24**(Suppl), 18-23.
- Robinson, M. R. G. (1987). Complete androgen blockade: the EORTC experience comparing orchiectomy versus orchiectomy plus cyproterone acetate versus low-dose stilboestrol in the treatment of metastatic carcinoma of the prostate. In *Prostate Cancer, Part A: Research, Endocrine Treatment, and Histopathology*, ed. Murphy, G. P., Küss, R., Khoury, S. *et al.* Pp. 383-390. New York: Alan R. Liss.
- Seely, J. E. (1987). Phase III studies in prostatic cancer with leuprolide acetate. *Radiology*, **8**, 5.
- Sharifi, R., Lee, M., Ojeda, L. *et al.* (1985). Comparison of leuprolide and diethylstilbestrol for stage D₂ adenocarcinoma of the prostate. *Urology*, **26**, 117-124.
- Smith, J. A. (1987). New methods of endocrine management of prostatic cancer. *J. Urol.*, **137**, 1-9.
- Soloway, M. S. and the Buserelin Protocol 301 Study Group. (1988). Efficacy of buserelin in advanced prostate cancer and comparison with historical controls. *Am. J. Clin. Oncol.*, **11**(Suppl.), S29-S32.
- Steg, R., Carlstrom, K., Collste, L. *et al.* (1989). Single-drug parenteral estrogen treatment in prostatic cancer: a study of two maintenance-dose regimens. *Prostate*, **14**, 183-188.
- Thompson, S. A., Rowley, D. R. and Heldger, P. M. (1979). Effects of estrogen upon the fine structure of epithelium and stroma in the rat ventral prostate gland. *Invest. Urol.*, **17**, 83-89.
- Trachtenberg, J., Halpern, N. and Pont, A. (1983). Ketoconazole: a novel and rapid treatment for advanced prostatic cancer. *J. Urol.*, **130**, 152-153.
- Tullner, W. W. (1963). Hormonal factors in the adrenal-dependent growth of the rat ventral prostate. *NCI Monogr.*, **12**, 211-223.
- Warner, B., Worgul, T. J., Drago, J. *et al.* (1983). Effect of very high dose d-leucine⁶-gonadotropin-releasing hormone proethylamide on the hypothalamic-pituitary testicular axis in patients with prostatic cancer. *J. Clin. Invest.*, **71**, 1842-1853.
- Waxman, J. (1988). A review of the Hammersmith Hospital, St. Bartholomew's Hospital and Institute of Urology studies of buserelin in advanced prostatic cancer. *Am. J. Clin. Oncol.*, **11**(Suppl 1), S16-S18.

The Author

E. D. Crawford, MD, Professor and Chairman, Division of Urology.

Requests for reprints to: E. D. Crawford, Division of Urology, University of Colorado Health Sciences Center, Campus Box C-319, 4200 East Ninth Avenue, Denver, CO 80262, USA.

Diagnostic Challenges of Prostatic Carcinoma

J. F. JIMÉNEZ-CRUZ and E. BROSETA

Service of Urology, La Fe Hospital, Valencia, Spain

Summary—The early detection and staging of prostatic carcinoma are challenging the diagnostic acumen of urologists. Mass screening programmes of asymptomatic men are not justified, as only a small number of cases are diagnosed when the tumour is confined to the prostatic capsule. Diagnostic work-ups of symptomatic men yield a similarly low rate of detection. The most extensively used diagnostic methods include digital rectal examination (DRE), transrectal ultrasound (TRUS) and prostate-specific antigen (PSA) assay. Although DRE is an inexpensive technique that improves early detection, its sensitivity and specificity are low. The specificity and sensitivity of TRUS are higher, but false-positive and false-negative rates are significant. In a study of 566 patients, the rates were 86% and 84%, respectively. A determination of PSA may be informative in the early stages of prostatic cancer, but confirmation of the results by other methods is necessary. Thus, there is no safe method to achieve early diagnosis and precise staging of prostatic carcinoma. Only clinical trials comparing all the different methods will help to establish the definitive role of each one.

The 2 important challenges that urologists face in the diagnosis of prostatic carcinoma are early detection and staging of the disease. The early detection of cancer has long been a goal, but why has it not been achieved? Only a small number of cases are diagnosed when the tumour is located within the prostate, whether such diagnosis occurs in the course of a mass screening programme or an office examination of symptomatic patients.

The screening of asymptomatic men is not generally accepted. Digital rectal examination (DRE), which has been implemented in some screening programmes, is inexpensive and improves early detection, but its sensitivity and specificity are low. Although DRE is the most sensitive screening test (Chodak and Schoenberg, 1984), it is associated with a low diagnosis rate. Additional methods are then necessary to obtain more accurate results, raising costs dramatically. On the other hand, what is the approach when cancer is detected, since more men die with prostatic cancer than die of it? Autopsies of men who died of other causes show that >30% of those >50 years old had occult prostatic carcinoma (Scardino, 1989). Unnecessary use of screening methods can produce morbidity, emotional and

physical trauma (especially in association with biopsy), incontinence, impotence and low mortality. For example, a mortality of 1% indicates that almost as many patients lost to treatment would be saved by screening (Chodak, 1989).

The sensitivity and specificity of all the screening methods currently in use cannot identify all men with prostate carcinoma. The cost:benefit ratio of mass screening programmes does not indicate an increase in the cure rate or mean survival of asymptomatic patients. In symptomatic patients, urological studies are clearly necessary; however, only a few cases show a tumour in an early stage and confined to the prostate.

Several methods for the diagnosis of prostate cancer have been proposed (Table 1). The most widely used methods are digital rectal examination, transrectal ultrasonography and prostate-specific antigen assay, which are the primary basis for this discussion.

Comparison of Diagnostic Methods

Digital rectal examination (DRE)

The positive predictive value of DRE is between 6% and 39% (Gerber and Chodak, 1990). On the

Table 1 Diagnostic Methods for Prostate Cancer

Digital rectal examination (DRE)
Transrectal ultrasonography (TRUS)
Computed tomography (CT)
Magnetic resonance imaging (MRI)
Bone scan
Tumour markers
Biopsy
Pelvic lymphadenectomy

other hand, 30–40% of the cancers detected by DRE can be expected to be localised within the prostate (Müeller *et al.*, 1988).

Transrectal ultrasound (TRUS)

In 1975, Watanabe *et al.* suggested the usefulness of TRUS in the diagnosis and staging of prostate cancer. They subsequently proposed its use in a mass screening programme (Watanabe *et al.*, 1984). However, others have regarded their own results as not showing the usefulness of TRUS in this context.

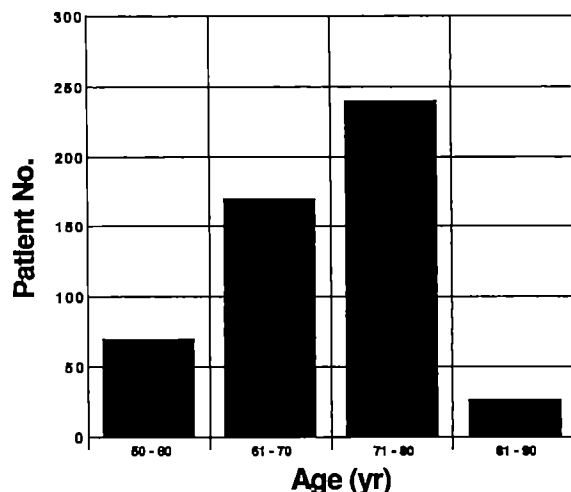
The interpretation of the sonographic patterns of prostatic cancer vary. Rifkin *et al.* (1983) believed that these patterns were mainly hyperechoic. Using 5-MHz probes, Lee *et al.* (1985) concluded that almost all tumours were hypoechoic. Considering echogenicity and other changes observed in prostates imaged by TRUS with a 7-MHz transducer, we have evaluated the results of our own study to determine the value of TRUS in patients with symptoms suggestive of prostatic disease and who do not represent a pure screening population (Table 2).

Patients and methods. A total of 566 patients who underwent histological examination of biopsy or surgical specimens had been examined first by DRE and then by TRUS. Histological findings were compared with those of DRE and TRUS to ascertain whether there was any correlation between the different modalities. All patients were >50 years old, with the majority between 60 and 80 years of age (Fig.).

Two groups of patients were studied: those with benign prostatic hyperplasia (BPH) (378) and those with prostatic cancer (188) clinically suspected by

Table 2 Evaluation of TRUS Patterns

Symmetry
Capsular disruption
TD/LD ratio <1.5
Echogenicity

**Fig.** Distribution of 566 patients with benign prostatic hyperplasia or prostatic cancer by age.

DRE. After the suspicious lesions were detected by DRE, TRUS was performed once or twice. If cancer was diagnosed by TRUS, a biopsy specimen was excised from the suspected area. The diagnoses obtained by DRE and TRUS were compared with the histological findings.

Sonographic signs in addition to echogenicity were considered in the TRUS evaluation (Table 2). In all cases, changes in the normal sonographic patterns of the prostate were found. The occurrence of hypoechoic areas in the BPH patients was less than that in the cancer patients. In keeping with this finding, asymmetry, capsular disruption and a transversal diameter (TD)/longitudinal diameter (LD) ratio <1.5 were more common in the cancer patients (Table 3).

When BPH was suspected after DRE, the histological study confirmed it in 366 of 378 patients. Twelve patients with incidental carcinoma were never identified by DRE, and TRUS only diagnosed 6 of them. Sensitivity was therefore 50%. In contrast, the sonographic pattern of patients with

Table 3 Sonographic Patterns of Cancer and BPH

	% Cancer	% BPH
Asymmetry	66	25.6
Capsular disruption	43.3	5.1
TD/LD ratio <1.5	56	19.2
Echogenicity		
Hypoechoic	60.8	35.5
Hyperechoic/isoechoic	39.1	64.5

Table 4 BPH Clinically Suspected by DRE in 378 Cases: TRUS and Histological Correlations

TRUS	Histological confirmation
324 BPH, 42 Ca	366 BPH
6 BPH, 6 Ca	12 Ca

Specificity, 88%; Sensitivity, 50%.

histological BPH suggested carcinoma in 42. Therefore, its specificity was 88% (Table 4).

Biopsy confirmed carcinoma in 126 of 188 patients clinically suspected by DRE. In the remaining 62, the histological examination of the resected tissue showed only BPH. In these patients, TRUS suggested carcinoma in 16 (specificity, 74%). In 126 histologically confirmed carcinoma patients, TRUS patterns indicated cancer in 110 (sensitivity, 87%) (Table 5).

When all patients in the study were considered, the specificity and sensitivity of TRUS were 86% and 84%, respectively (Table 6). Thus, our study showed significant false-positive and false-negative rates for early carcinoma detected by ultrasound. Hypoechoic areas like other sonographic changes can be secondary to artifacts or different prostatic pathoses. Therefore, TRUS is a relatively imprecise technique when used alone for the early diagnosis of prostatic carcinoma.

TRUS for staging. DRE is not a precise method in the staging of prostatic carcinoma. Volume of the tumour, location and extension can be determined, but when this information is compared with the histological findings on the removed tissue, the

results reveal a lack of precision. Other staging methods such as computed tomography or magnetic resonance imaging are expensive and limited in the information they yield about tumour pattern. TRUS is more accurate in distinguishing tumours within the prostate from those extending outside the gland. In this way, other sonographic changes apart from echogenicity are important. Asymmetry, modification of diameter, capsular disruption and extension into the seminal vesicles are more common in non-localised than in localised cancer (Table 7). However, understaging and overstaging with TRUS reduce the viability of this method (Andriole and Catalona, 1989).

Prostate-specific antigen (PSA)

Since PSA has improved sensitivity compared with prostatic acid phosphatase (PAP), this superiority suggests that PSA may be used in screening, staging and follow-up of patients with prostatic carcinoma. However, like cancer, prostatic hyperplasia elicits an elevated serum PSA. This similarity represents the main objection to the use of PSA for screening.

The PSA values that supposedly fall in the normal range remain controversial. Confidence intervals are obtained from an apparently normal population. However, given the prevalence of prostatic diseases, including occult carcinoma, it is probable that a significant number of "normal" men who were used as controls actually have some kind of prostatic disease. Therefore, the absence of a pathological finding cannot be established by a value within the normal range.

Of patients with prostatic carcinoma, 10–20% have PSA values in the normal range. Conversely, 5–88% of men with BPH have high levels of PSA. The range of this serum marker increases with the stage of the disease (Cooner *et al.*, 1988; Brawer

Table 5 Cancer Clinically Suspected by DRE in 188 Cases: TRUS and Histological Correlations

TRUS	Histological confirmation
46 BPH, 16 Ca	62 BPH
16 BPH, 110 Ca	126 Ca

Specificity, 74%; Sensitivity, 87%

Table 6 Histological Results in 566 Patients: TRUS Correlations

TRUS	Histological confirmation
370 BPH, 58 Ca	428 BPH
22 BPH, 116 Ca	138 Ca

Specificity, 86%; Sensitivity, 84%.

Table 7 Evaluation of Prostate Cancer in 138 Patients

	% Localised (n=29)*	% Non-localised (n=109)
Asymmetry	58	74
TD/LD <1.5	31	81
Capsular disruption	6.8	79.8
Echogenicity		
Hypoechoogenicity	65.5	56.2
Hyperechoogenicity/ isoechoogenicity	34.5	43.6
Seminal vesicle changes	0	12.8

*Six patients understaged.

and Lange, 1989). Sensitivity and specificity of PSA in prostatic carcinoma are directly related to normal values. Cooner *et al.* (1988) increased the specificity of PSA by using a cut-off value of PSA > 10 ng/ml in the diagnosis of cancer. However, its sensitivity is low—35.7%. With these values, the positive predictive value of a PSA level > 10 ng/ml is 75% for carcinoma, and the negative predictive value is 77%. As a result, PSA can be useful for screening, particularly in combination with other techniques like DRE and TRUS.

In staging, PSA viability is higher in extracapsular than in localised carcinoma because PSA levels increase with tumour volume. However, because of the wide range of PSA values in both localised and disseminated disease, it is not possible to select an upper limit for localised cancer without the risk of excluding those patients with gland-confined tumour.

Serum PSA is most useful in monitoring patients after radical prostatectomy. In the absence of prostatic cells, PSA should be equivalent to the serum level of women. However, in the early diagnosis of staging prostatic cancer, PSA alone is only informative and other methods are necessary to confirm the PSA results.

Discussion and Conclusions

From a clinical point of view, DRE has less sensitivity and specificity than TRUS. Therefore, it should not be considered the gold standard for the detection of prostate cancer.

There is currently no technique, alone or in combination, that eliminates the possibility of understaging or overstaging prostatic cancer. Probably TRUS is the most precise method in the evaluation of local extension of cancer. With the use of 7-MHz probes accommodating needle channels, TRUS allows biopsies to be performed via the transrectal route. Therefore, specimens from small intraprostatic lesions and other areas of potential microscopic cancer extension, like pericapsular tissue and/or seminal vesicles, may be excised under sonographic control. This method reduces the rate

of diagnostic error. However, there are still patients who do not receive correct staging.

As a single modality for the diagnosis and staging of early prostatic carcinoma, PSA is informative rather than definitive and must be supplemented with other studies to confirm its results.

References

- Andriole, G. L. and Catalona, W. J. (1989). Transrectal ultrasonography in the staging of prostate cancer. In *Diagnostic ultrasound of the prostate*, eds. Resnick, M. R., Watanabe, H. and Karr, J. P. Pp. 25–30. New York: Elsevier.
- Brawer, M. K. and Lange, P. H. (1989). Prostate-specific antigen in management of prostatic carcinoma. *Urology*, **33** (Suppl), 11–16.
- Chodak, G. W. (1989). Early detection and screening for prostatic cancer. *Urology*, **34** (Suppl), 10–12.
- Chodak, G. W. and Schoenberg, H. W. (1984). Early detection of prostate cancer by routine screening. *JAMA*, **252**, 3261–3264.
- Cooner, W. H., Mosley, B. R., Rutherford, C. L., Jr. *et al.* (1988). Clinical application of transrectal ultrasonography and prostate specific antigen in the search for prostate cancer. *J Urol.*, **139**, 758–761.
- Gerber, G. S. and Chodak, G. W. (1990). Digital rectal examination in the early detection of prostate cancer. *Urol. Clin. North Am.*, **17**, 739–744.
- Lee, F., Gray, J. M., McLeary, R. D. *et al.* (1985). Transrectal ultrasound in the diagnosis of prostate cancer: location, echogenicity, histopathology, and staging. *Prostate*, **7**, 117–129.
- Müller, E. J., Crain, T. W., Thompson, I. M. *et al.* (1988). An evaluation of serial digital rectal examinations in screening for prostate cancer. *J. Urol.*, **140**, 1445–1447.
- Rifkin, M. D., Kurtz, A. B., Choi, H. Y. *et al.* (1983). Endoscopic ultrasonic evaluation of the prostate using a transrectal probe: prospective evaluation and acoustic characterization. *Radiology*, **149**, 265–271.
- Scardino, P. T. (1985). Early detection of prostate cancer. *Urol. Clin. North Am.*, **16**, 635–655.
- Watanabe, H., Igari, D., Tanahashi, Y. *et al.* (1975). Transrectal ultrasonography of the prostate. *J. Urol.*, **114**, 734–739.
- Watanabe, H., Ohe, H., Inabe, T. *et al.* (1984). A mobile mass screening unit for prostatic disease. *Prostate*, **5**, 559–565.

The Authors

J. F. Jiménez-Cruz, MD, Head of Service
E. Broseta, MD, Consulting Urologist.

Requests for reprints to: J. F. Jiménez-Cruz, Service of Urology, La Fe Hospital, Avda Campanar 19, 46010 Valencia, Spain.

Postsurgical Management of the Patient Undergoing Radical Prostatectomy

F. SOLE-BALCELLS, H. VILLAVICENCIO and A. ORTIZ

Puigvert Foundation, Barcelona, Spain

Summary—Radical prostatectomy is a useful procedure for the treatment of prostate cancer limited to the gland; however, failure may occur as a result of the immediate or delayed complications of surgery, or to disease recurrence related to incomplete tumour excision. Seventy-nine radical prostatectomies were performed between April 1985 and August 1991 in patients with prostate cancer (primarily stage B1) who averaged 63 years of age. Immediate post-operative complications included vesicocutaneous fistulae, cystic lymphangiomas, abdominal wall abscesses, extraperitoneal haematoma, acute cholecystitis, and enterocutaneous fistula. Massive pulmonary embolism accounted for 2 deaths. Of the 77 surviving patients followed up for an average of 34 months, 79.2% (61) were continent, 15.6% had stress-related incontinence or severe incontinence and 5.2% were lost to follow-up. Sexual potency was preserved in 13 of the 33 patients (39%) who were pre-operatively potent. A favourable outcome as defined by no recurrence was seen in 69 patients (87.3%). Four patients (5.1%) are living with recurring prostatic cancer and 1 patient has died of the disease 46 months after surgery.

Radical prostatectomy is achieving increasing credibility as a treatment for patients whose prostate cancer is limited to the gland. Nevertheless, such intervention may be followed by failures either due directly to the immediate or delayed complications of surgery or to incomplete excision of tumour, in which case cancer-positive margins at the excision site or neoplastic infiltration by local and/or regional adenopathies leads to relapse *in situ* or to distant metastases (Pavone-Macaluso, 1989).

Patients and Methods

At the Puigvert Foundation in Barcelona, Spain, 79 radical prostatectomies were performed between April 1985 and August 1991 in patients who averaged 62.9 years of age (range, 50–75 years). The pre-operative categorisation of clinical stages was as follows: A1, 2 patients; A2, 9; B1, 62; and C, 6 patients. The post-operative categorisation of histopathologically confirmed stages was T0, 4; B, 23; C, 45; and D, 7 patients. Thus, the correlation between clinical and histopathological data was 29.1%, with a 65.8% clinical underestimation of

stage and a 5% overestimation of stage (T0, 4 patients) (Table).

In 14 (17.7%) of the patients, some degree of stenosis developed at the urethrovesical junction. All patients were treated by means of endoscopic cystotomy, with 2 requiring a second intervention.

Massive pulmonary thromboembolism was responsible for 2 cases of postoperative mortality, which occurred 12 and 18 days, respectively, after surgical intervention. Immediate post-operative complications and their subsequent treatment were as follows: vesicocutaneous fistulae (3 patients),

Table Correlation Between Clinical and Histopathological Data

	T0	A1	A2	B	C	D1	Total
A1	1			1			2
A2	2			2	5		9
B	1			20	37	4	62
C					3	3	6
D1							—
Total	4			23	45	7	79

which were closed with permanently implanted urethral catheters; cystic lymphangiomas (3 patients), which did not necessitate any follow-up intervention; abdominal wall abscesses (2 patients) and extraperitoneal haematoma (1 patient), which were surgically drained; acute cholecystitis (1 patient), which necessitated emergency intervention; and enterocutaneous fistula (1 patient), which healed spontaneously.

Patients were followed up for an average of 34 months (range, 2–75 months). Of the 77 surviving patients, 79.2% (61) were continent at the end of the study, 15.6% (12) had stress-related incontinence and/or severe incontinence and 5.2% (4) were lost to follow-up. Sexual potency was preserved in 13 of the 33 patients who were potent before the surgery.

Assays to determine the level of prostate-specific antigen (PSA) were performed in 49 patients; of this group, 3 patients were found to have increased levels of PSA. A favourable outcome as defined by no recurrence of disease was seen in 69 patients (87.3%). In contrast, 4 patients (5.1%) are living with prostatic cancer, and only 1 patient has died of the disease 46 months after surgery.

Discussion

The occurrence of treatment failure (*i.e.*, morbidity and mortality) after radical prostatectomy for prostate cancer depends on the age and clinical state (*e.g.*, concurrent diseases and immunological response) of the patient, tumour stage and grade, previous treatment (*e.g.*, transurethral resection) and the experience of the surgeon and the technique selected.

In our experience the incidence of immediate complications was 7.7%. In a study by Rossignol *et al.* (1991), the overall incidence was 6.9%. The most frequent complications cited by this group were thrombophlebitis of the lower limbs (2.3%) and lymphoceles (2.3%), followed by haematoma caused by surgical wound infection (0.95%) and pulmonary thromboembolism (0.8%). Late complications of radical prostatectomy include urinary incontinence, loss of sexual potency and sclerosis of the urethrovessical junction.

Urinary incontinence

In our experience, urinary incontinence in the aftermath of prostatectomy varied from 0.5% to

11%, depending on how this symptom had been rated by the patient. The number of absorbent liners worn daily and the extent to which this situation is socially acceptable to the patient are factors in the symptom assessment.

Lange *et al.* (1990a) reported a 100% incidence of continence in 50 patients 1 month after surgical intervention with radical prostatectomy. Although the majority of authors concur that urinary continence improves with the passage of time (O'Donnell *et al.*, 1990b), incontinence will persist for a lengthier period if it is extremely problematic immediately after the surgery.

Of 250 patients who underwent radical prostatectomy in a study reported by Catalona and Bigg (1990), 192 were followed up for 6 months after surgery. The investigators noted that urinary continence was achieved in 188 patients (98%).

Brendler *et al.* (1991), who analysed 600 cases of radical prostatectomy, pointed out that the percentage of patients achieving continence after surgery was 47% at 3 months, 89% at 12 months, and 92% at 2 years. The incidence of stress-related incontinence was 8%. Total incontinence was nil.

Analysis of the causes of urinary incontinence has not yielded any relationship between this symptom and a patient's age, prostate weight, tumour stage or previous transurethral resection. According to O'Donnell and Finan (1989), the incidence of post-surgical incontinence clearly differs if a nerve-sparing technique is successfully implemented. With neurovascular preservation, the incidence of total incontinence was 0% while the incidence of stress-related incontinence was 6%; without it, these percentages were 12% and 18%, respectively. Some authors have found a higher incidence of incontinence among those patients with prostate cancer who had previously undergone transurethral resection, or in those patients who were treated with radiotherapy after transurethral resection (Green *et al.*, 1990).

Schulman *et al.* (1991) noted that recovery of urinary continence after radical prostatectomy is faster if androgen deprivation therapy is pre-operatively administered. Patients who received such therapy were continent 3 months post-operatively. Without androgen deprivation, patients were not continent until 9 months later.

To explain the mechanism whereby incontinence occurs after radical prostatectomy, it is essential to remember that passive urinary control is maintained by the striated sphincter of the urethra, which is compressed mainly in the anterior portion of the urethra. Ligation of the deep venous plexus

may cause an injury to this musculature. For this reason, Walsh *et al.* (1990) and Brendler *et al.* (1991) have asserted that it is necessary to recognise the striated sphincter and to fasten it transversely to the borders of the venous complex. With this approach, the external sphincter will remain joined to the neck of the urinary bladder when urethrovesical anastomosis is performed. Since using this technique in addition to the eversion of the mucosal borders of the newly formed neck of the urinary bladder, Walsh *et al.* (1990) have obtained a 73% continence rate 3 months after surgery in the past 113 patients, in comparison with a 47% continence rate in patients not undergoing this technique.

O'Donnell and colleagues (1990a) placed a haemoclip to the urethrovesical anastomosis in 8 cases of radical prostatectomy. By performing post-operative urinary cystourethrograms, they have observed that the functional level of continence is situated at a distance of 9 mm from the site of the anastomosis.

Presti *et al.* (1990) point out the importance of tubularisation in the anastomotic zone; those patients whose posterior urethra has a length of 2.8 cm are continent, whereas those whose posterior urethra measures only 1.2 cm are incontinent due to lack of tubularisation. By closing the vesical opening in the form of a "tennis racket handle" the surgeon succeeds in closing the median layer of the circular fibres of the bladder neck, which results in this tubularisation (Fig. 1).

Sclerosis of the neurovesical anastomosis

Reconstruction of the bladder floor in the manner of a "tennis racket," with eversion of the vesical mucosa, diminishes the incidence of sclerosis affecting the anastomotic zone as a late post-operative complication. In our series of patients, the incidence of stenosis at the urethrovesical junction was 17.7%; other statistical surveys have shown lower rates such as 9.6% (Becht *et al.*, 1991) and 11.5% (Surya *et al.*, 1990). Surya *et al.* point out that factors conducive to the development of this type of stenosis are extensive intra-operative blood loss, extravasation of urine due to failure of the anastomosis and previous transurethral resection. Incision of the urethrovesical fibrous zone should be accomplished with a cold knife. Alternative use of electrocautery has been associated with a high incidence of incontinence (Surya *et al.*, 1990).

Sexual potency

Advancements in "nerve-sparing" technique have

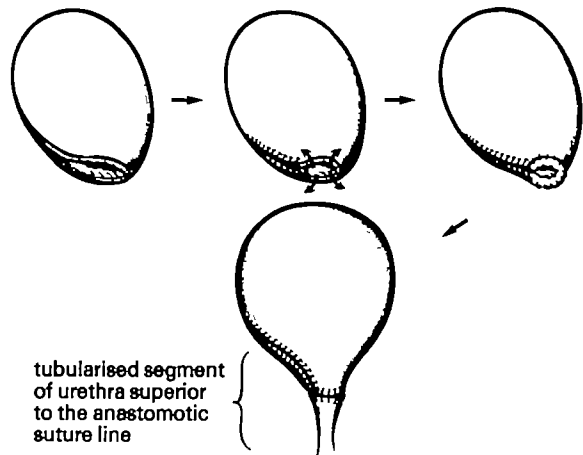


Fig. 1 Tubularisation of the anastomotic zone of the bladder.

made the preservation of sexual potency after radical prostatectomy possible. The largest patient series involving the use of the nerve-sparing technique are those of Catalona and Bigg (1990) and Walsh (1991). Catalona and Bigg (1990) reported that sexual potency was preserved in 71 of 112 patients (63%) who had undergone bilateral preservation of the neurovascular bundles but in only 13 of 33 patients (39%) who had undergone unilateral preservation. Walsh (1991) reported preserved sexual potency rates of 88% and 19%, respectively, for the bilateral and unilateral nerve-sparing techniques. He emphasised the importance of age, as potency is preserved in 91% of men who are <50 years of age but in only 25% of men who are >75 years of age.

Recurrent disease

Radical prostatectomy fails in its objective to completely eradicate prostate cancer when tumour persists in the pelvic plane or infiltrates the local and/or regional lymphatic ganglia. The infiltration or invasion of the prostatic capsule and the presence of positive surgical margins are significant factors in treatment failure.

Prostate cancer is considered to be organ confined when there is no infiltration of the prostatic capsule. When either capsular infiltration without penetration or seminal vesical invasion is present, and surgical margins are negative, then the disease is tumour confined. If there is infiltration into the periprostatic tissues, then the surgical margins are positive (Fig. 2).

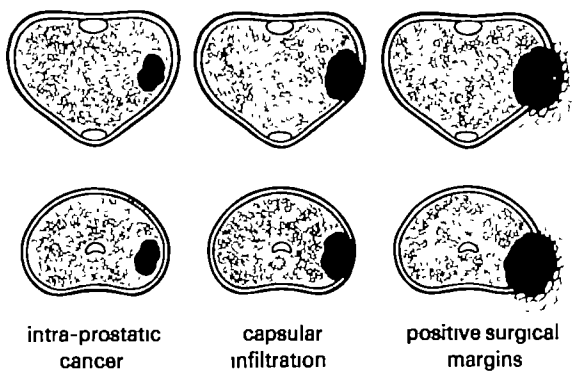


Fig. 2 Extent of prostatic cancer

Accurate staging of prostate cancer is fundamental to predicting local recurrence, which is defined as tumour confined within the extirpated specimen. Brendler *et al.* (1991) reported a 5-year local recurrence rate of 2% in patients with organ-confined disease; 8% in those with capsular penetration; 8% in those with cancer-positive margins, with 1% of distant metastases in patients with intraprostatic cancer; 1% in those with capsular invasion; and 19% in those with cancer-positive surgical margins. In the presence of elevated serum prostatic acid phosphatase (PAP) levels, the rates of local recurrence were 3%, 16% and 41%, respectively, in patients with organ-confined disease, with capsular penetration, and with cancer-positive margins.

In the experience of Walsh (1991), failure after radical prostatectomy was evident by a 36% rate of neoplastic penetration into the prostatic capsule, a 10% rate of positive surgical margins, a 13% rate of seminal vesicle invasion and a 7% rate of positive ganglia in 414 biopsy specimens.

Stamey *et al.* (1990) examined the surgical margins of 189 clinical stage B tumour specimens obtained during radical prostatectomy. Their study revealed that 31 of 136 patients (23%) had positive margins; 17 (55%) of the 31 surgically positive margins were located at the apex, a zone that is beyond the prostatic capsule.

The finding of positive-margin disease is of importance with respect to the volume of the cancer and the number of zones that have been invaded. In the study by Stamey *et al.* (1990), it was noted that if a tumour was larger than 12 cc, then invasion into the seminal vesicles and the local and/or regional ganglia, and multiple positive margins were encountered. The relationship between tu-

mour volume and capsular penetration was evident in a study by Donohue (1991), which showed a capsule infiltration rate of 16% with tumours <1 cc, 66% with tumours 1.3 cc and 95% with tumours >3 cc.

In contrast, the presence of positive-margin disease may not be associated with an elevated serum PAP level until 5 years of tumour growth (Stamey *et al.*, 1990). A relationship exists between the grade of the tumour and capsule penetration: 15% in grade II, 50% in grade III and 87% in grade IV (Donohue, 1991).

The frequency and extent of cancer-positive margins do not significantly differ between specimens obtained by standard radical retropubic prostatectomy and those obtained by nerve-sparing technique (Jones, 1990; Wahle *et al.*, 1990). In a comparative study of the 2 techniques, Jones noted no difference in frequency but pointed to a direct relationship between the presence and extent of positive surgical margins with tumour size. Likewise, Wahle *et al.* (1990) showed that in 20 nerve-sparing and 30 radical retropubic prostatectomies, the positive-margin rates were 45% and 30%, respectively. This finding does not represent a significant difference, suggesting that the nerve-sparing technique does not change the outcome when tumour extirpation by prostatectomy is the proposed treatment.

In our experience, clinical understaging of prostate cancer in stage C occurred in 66.1% of patients. That is, of 62 patients presumed to be stage B, only 20 (32%) were pathologically confirmed as stage B; 37 (60%) were actually stage C, 4 (6%) were stage D, and 1 was T0.

The presence of a positive surgical margin is not synonymous with invasion of the neurovascular bundle. In 40 cases of radical prostatectomy, Epstein (1990) extirpated the bundle from 10 patients with a positive margin to obtain a second surgical specimen. Of these 10 bundles, only 6 were positive. In the same study, there were 11 patients with tumour extending up to the dye-stained margin, but none had evidence of tumour in the bundle.

Neither pre-operative determination of the serum PAP or PSA level, nor echography is of value for predicting extracapsular extension. Rather, it is the presence of a tumour that is poorly differentiated or considerable in volume that should lead one to suspect that the surgical margin may be positive (Bigg *et al.*, 1990). These 2 factors have been correlated with a high incidence of positive margins.

An extraordinarily wide disparity of opinion exists in regard to which procedure should be used when tumour penetration into the capsule and/or positive surgical margins are encountered. According to some authors, penetration into the capsule does not necessitate the administration of treatment because the survival rate of patients so affected does not significantly vary in comparison with the rate of patients without such invasion. For example, the 5-year survival for tumour-free patients is 85%, and the 10-year survival for patients with capsular invasion is 70% (Farrow *et al.*, 1991). Progression of prostate cancer more closely correlates with a high Gleason grade than with capsular invasion (Farrow *et al.*, 1991).

Numerous studies have reported that radiotherapy administered adjunctively reduces the risk of local recurrence without affecting post-operative continence or sexual potency (Auscher and Prosnitz, 1990; Farrow *et al.*, 1991). In the study by Douchez *et al.* (1991), the risk of recurrence was only 4.1%. When administered after radical prostatectomy, radiotherapy can effect a decrease in an elevated PAP level (Morgan *et al.*, 1991). In a study by Lange *et al.* (1990b), 82% of patients experienced a reduction of >50% in the serum PAP level, with 43% attaining values <0.4 ng/ml. These data suggest that radiotherapy achieves local and/or regional control of the disease; however, the duration and precise therapeutic value of these effects are not known.

A serum PAP determination is useful for detecting subclinical local recurrence of persistent tumour in the prostatic bed, as well as for monitoring the response to treatment (Keisch *et al.*, 1990). Radiotherapy was administered to 21 patients with an elevated serum PAP level after radical prostatectomy. As a result, 29% experienced a decrease in PAP to undetectable levels and were free of disease for an average period of 12.6 months. Disease progressed in 7 of the 13 patients whose PAP level remained unchanged (Hudson and Catalona, 1990). In a follow-up study of 159 cases of positive-margin disease after radical prostatectomy, Paulson *et al.* (1990) did not find any benefit conferred upon patients who had radiotherapy in comparison with those who were not so treated.

Orchiectomy has also been recommended as an adjunctive treatment when residual tumour is found after radical prostatectomy. Leitenberger *et al.* (presented at the 22nd Congress of the Societ  International d'Urologie, Seville, Spain, 1991) undertook a comparative analysis of 35 patients with untreated positive-margin disease and saw a

5-year survival rate of 90% in comparison with a 62% rate in patients given adjunctive treatment. Thus, the difference in survival was not significant. Adjunctive treatment does not appear to prolong the survival, but it does influence the duration of illness and the quality of life.

In summary, patients with positive surgical margins and/or an elevated serum PAP level after radical prostatectomy appear to benefit from adjunctive radiotherapy for control of local and/or regional disease and for prolongation of the disease-free interval. However, the efficacy of radiotherapy in increasing patient survival is unclear. It may be advantageous to combine radiotherapy with hormonal therapy in these patients.

To monitor local progression of disease after radical prostatectomy in those patients with previously documented invasion of the prostatic capsule and infiltration of surgical margins or the seminal vesicles, PAP level determinations, transrectal ultrasonography (TRUS) (Parra *et al.*, 1990), and especially TRUS-guided needle biopsy in the urethrovesical zone have been performed post-operatively. Lightner *et al.* (1990) found that in 57 patients without evidence of disease by the usual detection methods (*e.g.*, digital rectal examination), 42% (24) had positive needle biopsy specimens confirming local disease after radical prostatectomy. Similarly, recent studies point out the limited value of detection methods such as computed tomography and magnetic resonance imaging for the prediction of capsular invasion (Quintens *et al.*, 1990).

Local regional lymph node invasion in radical prostatectomy

Walsh (1991) cited a 7% incidence of cancer-positive nodes among 414 patients who had undergone radical prostatectomy. Paulson noted that recurrent disease in the form of microscopic invasion of the lymph node or margin-positive disease occurred at an equal rate (1991). Hering *et al.* (1990) also noted that when only 1 cancer-positive node was involved, the associated 10-year disease-free survival rate was 65%; however, in the event of bilateral infiltration into the lymphatic system, the survival rate was 0%.

The opinions concerning the selection of prostatic cancer treatment when invasion of the lymph nodes has been demonstrated are likewise divided. Walsh (1991) saw no evidence that early hormonal treatment prolonged survival and consequently does not recommend its use until disease progresses. De-

Kernion *et al.* (1990) have conducted a study in patients with cancer-positive nodes who had previously undergone radical prostatectomy and were later randomised to receive early hormonal treatment or observation only. Both patient groups were homogeneous with respect to age range, Gleason grade, tumour volume and pathological stage. Although these investigators did not find a significant difference in survival rate between the hormonal treatment and the observation-only groups (91% versus 71%, respectively), they did observe a longer disease-free period with hormonal treatment (67% versus 32% after 9 years). They deduced that early hormonal treatment after radical prostatectomy has a palliative effect in cases of nodal invasion and especially in cases of small tumour-volume, as evidenced by the longer disease-free interval.

References

- Anscher, M. S. and Prosnitz, L. R. (1990). Postoperative radiotherapy of the prostate for patients undergoing radical prostatectomy with positive margins, seminal vesicle involvement and/or penetration through the capsule. *J. Urol.*, **143**, 1238.
- Becht, E., Moll, V., Zwergel, Th., *et al.* (1991). Radical prostatectomy versus voltage radiotherapy in the treatment of the locoregional prostatic carcinoma. In: Program and abstracts of the 22nd Congress of the Société Internationale d'Urologie, Abstract No 329; Sevilla, Spain.
- Bigg, S. W., Kavoussi, L. R. and Catalona, W. J. (1990). Role of nerve-sparing radical prostatectomy for clinical stage B2 prostate cancer. *J. Urol.*, **144**, 1420-1424.
- Brendler, C. B., Morton, R. A., Steiner, M. S. *et al.* (1991). Cancer control and urinary continence following anatomical radical prostatectomy. *Urol. Clin. North Am.*, **108**, 113.
- Catalona, W. J. and Bigg, S. W. (1990). Nerve-sparing radical prostatectomy: evaluation of results after 250 patients. *J. Urol.*, **143**, 538-544.
- de Kernion, J. B., Neuwirth, H., Stein, A. *et al.* (1990). Prognosis of patients with stage D₁ prostate carcinoma following radical prostatectomy with and without early endocrine therapy. *J. Urol.*, **144**, 700-703.
- Donohue, R. E. (1991). Radical prostatectomy: experience with pelvic lymphadenectomy and whole amount of the removed prostate. In: Program and abstracts of the 22nd Congress of the Société Internationale d'Urologie; Abstracts No 328; Sevilla, Spain.
- Douchez, J., Bachand, J. M., Izar, F., *et al.* (1991). Adjuvant radiotherapy after radical prostatectomy: tolerance and preliminary report. In: Program and abstracts of the 22nd Congress of the Société Internationale d'Urologie; Abstract No 330; Sevilla, Spain.
- Epstein, J. J. (1990). Evaluation of radical prostatectomy capsular margins of resection: the significance of margins designated as negative closely approaching, and positive. *Am. J. Surg. Pathol.*, **14**, 626-632.
- Farrow, G. A., Robinette, M. A. and Bulbul, M. A. (1991). Significance of pathological stage in long term follow-up of radical prostatectomy. In: Program and abstracts of the 22nd Congress of the Société Internationale d'Urologie, Abstract No 318, Sevilla, Spain.
- Green, N., Treble, D. and Wallack, H. (1990). Prostate cancer: post-irradiation incontinence. *J. Urol.*, **144**, 307-309.
- Hering, F., Rist, M., Roth, J. *et al.* (1990). Does microinvasion of the capsule and/or micrometastases in regional lymph nodes influence disease-free survival after radical prostatectomy? *Br. J. Urol.*, **66**, 177-181.
- Hudson, M. A. and Catalona, W. J. (1990). Effect of adjuvant radiation therapy on prostate specific antigen following radical prostatectomy. *J. Urol.*, **143**, 1174-1177.
- Jones, E. C. (1990). Resection margin status in radical retropubic prostatectomy specimens: relationship to type of operation, tumor size, tumor grade and local tumor extension. *J. Urol.*, **144**, 89-95.
- Kelsch, M. E., Perez, C. A., Grigsby, P. W. *et al.* (1990). Preliminary report on 10 patients treated with radiotherapy after radical prostatectomy for isolated elevation of serum PSA levels. *Int. J. Radiol. Oncol. Biol. Phys.*, **19**, 1503-1506.
- Lange, D., Bruce, W. and Grellier, P. (1990a). Les elements du diagnostic precoce e du bilan d'extension du cancer prostatique Resultats fonction de l'intervention radical. A propos de cinquante prostatectomies totales. *Ann. Urol.*, **24**, 103-108.
- Lange, P. H., Lightner, D. J., Medini, E. *et al.* (1990b). The effect of radiation therapy after radical prostatectomy in patients with elevated prostate specific antigen levels. *J. Urol.*, **144**, 927-933.
- Leitenberger, A., Baur, H. and Altwein, J. E. (1991). Adjuvant treatment after radical prostatectomy. In: Program and abstracts of the 22nd Congress of the Société Internationale d'Urologie; Abstract No 39; Sevilla, Spain.
- Lightner, D. J., Lange, P. H., Reddy, P. K. *et al.* (1990). Prostate specific antigen and local recurrence after radical prostatectomy. *J. Urol.*, **144**, 921-926.
- Morgan, W. R., Zincke, H., Rainwater, L. M. *et al.* (1991). Prostate specific antigen values after radical retropubic prostatectomy for adenocarcinoma of the prostate: impact of adjuvant treatment (hormonal and radiation). *J. Urol.*, **145**, 319-323.
- O'Donnell, P. D., Brookover, T., Hewett, M. *et al.* (1990a). Continence level following radical prostatectomy. *Urology*, **36**, 511-512.
- O'Donnell, P. D. and Finan, B. F. (1989). Continence following nerve-sparing radical prostatectomy. *J. Urol.*, **142**, 1277-1280.
- O'Donnell, P. D., Finan, B. F., Barnett, T. *et al.* (1990b). Continence recovery following radical prostatectomy. *Neuro-Urol. Urodynamics*, **9**, 251-256.
- Parra, R. O., Wolf, R. M. and Huben, R. P. (1990). The use of transrectal ultrasound in the detection and evaluation of local pelvic recurrences after a radical urological pelvic operation. *J. Urol.*, **144**, 707-709.
- Paulson, D. (1991). Radical prostatectomy for clinically confined prostatic cancer. In: Program and abstracts of the 22nd Congress of the Société Internationale d'Urologie; Abstract No 36; Sevilla, Spain.
- Paulson, D. F., Moul, J. W., Robertson, J. E. *et al.* (1990). Postoperative radiotherapy of the prostate for patients undergoing radical prostatectomy with positive margins, seminal vesical involvement and/or penetration through the capsule. *J. Urol.*, **143**, 1178-1182.
- Pavone-Macaluso, M. (1989). Analysis of failures of radical prostatectomy. *Acta Urol. Ital.*, **5**, 439-441.

- Presti, J. C. Jr., Schmidt, R. A., Narayan, P. A. *et al.* (1990). Pathophysiology of urinary incontinence after radical prostatectomy. *J. Urol.*, **143**, 975-978.
- Quintens, H., Chevallier, D., Michels, J. F. *et al.* (1990) Le scanner et l'IRM peuvent-ils predire l'envahissement capsulaire des cancers de prostate localises? Stude de vingt prostatectomies radicales *Ann. Urol.*, **24**, 335-339
- Rosignol, G., Leandrin, P., Ramon, J., *et al.* (1991). Morbidity of radical prostatectomy: review of 620 consecutive cases. In: Program and abstracts of the 22nd Congress of the Societé International d'Urologie; Abstract No 37, Sevilla, Spain.
- Schulman, C. C., Sassine, A. M., Vanden Borsche, M., *et al.* (1991). Role of hormonal therapy before radical prostatectomy. In: Program and abstracts of the 22nd Congress of the Societé International d'Urologie; Abstract No 336; Sevilla, Spain
- Staney, T. A., Villers, A. A., McNeal, J. E. *et al.* (1990). Positive surgical margins at radical prostatectomy: importance of the apical dissection. *J. Urol.*, **143**, 1166-1173
- Sarya, B. V., Provet, J., Johanson, K-E. *et al.* (1990) Anastomotic strictures following radical prostatectomy: risk factors and management. *J. Urol.*, **143**, 755-758.
- Wahle, S., Reznicek, M., Fallon, B. *et al.* (1990). Incidence of surgical margin involvement in various forms of radical prostatectomy. *Urology*, **36**, 23-26.
- Walsh, P. C. (1991) Radical prostatectomy: experience with 1100 cases. Presented at the XXIII Congresso Brasileiro de Urologia; October 21, 1991; Recife, Brasil.
- Walsh, P. C., Quinlan, D. M., Morton, R. A. *et al.* (1990). Radical retropubic prostatectomy: improved anastomosis and urinary continence. *Urol Clin North Am.*, **17**, 679-684

The Authors

F. Sole-Balcells, MD, Director of Education.

H. Villavicencio, MD, Chief of Oncological Urology Division.

A. Ortiz, MD, Resident.

Requests for reprints to: F. Sole-Balcells, Director of Education, Fundacion Puigvert, Cartagena, 340-350, 08025 Barcelona, Spain.

Management of Stage C Adenocarcinoma of the Prostate

J. H. LYNCH, and C. W. GRAHAM

Division of Urology, Georgetown University, Washington, DC, USA.

Summary—A review of numerous clinical series dealing with the treatment of patients with clinical stage C prostate cancer failed to find the treatment or a combination of treatments that is superior to any other. Accurate staging, which was difficult in older studies, and stage migration, which complicates the comparison of recent to older studies, may contribute to this lack of identification. The majority of patients ultimately experience disease progression and are therefore treated with hormonal therapy, the use of which obscures survival data for initial modes of treatment. These observations point to the need for control of randomised clinical trials to identify effective treatments in the future.

Natural History

The natural history of prostate cancer has been studied by observation of the progression of untreated patients and by interpretation of the pathology data from prostatectomy and necropsy specimens. In a study in Sweden, localised prostate cancer (T0–T2) patients were not treated until disease progression. Only 19 (8.5%) of the 223 patients had died of prostate cancer; 105 (85%) had died from other causes. The 10-year, disease-specific survival rate was 86.8%, which was the same (87.9%) as in a subgroup of 58 patients who met current indications for radical prostatectomy. The relative risk (hazard) of dying of prostate cancer was 58.4 times higher in patients with poorly differentiated grade 3 tumours than in those with highly differentiated grade 1 tumours (Johansson *et al.*, 1992).

Pathology studies have shown a direct correlation between cancer volume, local extension and metastatic disease; capsular penetration is associated with a 50% 8-year progression rate (Mukamel *et al.*, 1990). High-grade tumours correlate with all these poor prognostic indicators and with progression. Essentially, the majority of cancerous lesions >12 cm³ in volume have the poor prognostic features of seminal vesicle invasion, lymph node metastases and multiple positive margins (Stamey

et al., 1990). On the other hand, tumours <4 cm³ rarely metastasise (McNeal *et al.*, 1986).

The extent of capsular involvement by cancer has prognostic significance, with minimal involvement having little effect on survival, while penetration rivals seminal vesicle invasion in terms of increased risk of disease progression (Mukamel *et al.*, 1990; Villers *et al.*, 1990). There is 1 report that capsular penetration <1 cm in length may not adversely affect survival (Stamey *et al.*, 1989). Using the nerve-sparing technique, Stamey *et al.* (1989) found that approximately half of capsular penetrations were at the prostatic apex, a quarter on the rectal or lateral sides, and a quarter at the bladder neck or superior pedicle. Almost all the apical extensions were along the nerve bundles in the inferior pedicle (Stamey *et al.*, 1990). The likelihood of a tumour invading the seminal vesicles is related to its proximity to the prostatic midbase; the route of invasion is along the muscular wall of the ejaculatory duct rather than through the capsule (Villers *et al.*, 1990).

Staging

Stage C tumours are those that have penetrated through the prostatic capsule and have invaded the seminal vesicles or other adjacent organs. Catalona

and Scott (1986) reported that a single positive node found at radical prostatectomy is associated with a 50% 5-year disease-free progression rate and suggests that a T0-3N1M0 lesion is stage C disease.

The most recent data on staging errors have been derived from pathological correlations of specimens excised from patients with clinically localised disease who underwent radical prostatectomies with lymph node dissections. Understaging of disease is frequent; local extension is found rarely in clinical stage A1, 11–50% in clinical stage A2, 17–43% in stage B1, and 39–66% in stage B2 (Catalona and Stein, 1982; Lange and Narayan, 1983). In patients with T3 (pT3) disease, positive lymph nodes were found in approximately 50%; positive nodes were more common when seminal vesicle invasion was present than when capsular penetration alone was present (Catalona and Stein, 1982; Lange and Narayan, 1983). In comparison, positive lymph nodes were discovered in 39–46% of patients with clinical stage C disease (Catalona and Scott, 1986). Pathological downstaging of stage C patients has been reported to be as high as 30% (Catalona and Scott, 1986).

Staging errors result because of inadequacies in the various staging modalities. As pathological correlations are necessary to assess tumour stage, studies evaluating staging techniques primarily report on low-stage patients. Several methods are used to help assess whether locally advanced disease is present. Those patients with obvious local extension or known metastatic disease seldom undergo an operation and thus are excluded from the studies. The result is that the accuracy of the staging methods is underestimated; however, it is the elusive local extension and metastases that warrant the search for better characterisation of prostate cancers and render the limitations of these studies somewhat inconsequential.

Staging methods

Digital rectal examination (DRE). The DRE discriminates poorly between stage B and early stage C lesions, and it cannot predict the size of tumour nodules accurately (Palken *et al.*, 1990).

Transrectal ultrasound of the prostate (TRUS). Studies evaluating TRUS as a staging tool vary in their conclusions. Palken *et al.* (1990) discovered that TRUS estimates were within 25% of whole-mount measurements in most patients. Others evaluating TRUS for detection of local extension have reported sensitivities of 57–86% with specificities of 78–100% (Andriole *et al.*, 1988). It has been

suggested that when local invasion is seen, TRUS is superior to DRE for the diagnosis of stage C disease (Andriole *et al.*, 1988; Perrapato *et al.*, 1989). It also has potential for systematically directing biopsies of the prostate and seminal vesicles to improve staging accuracy.

Several TRUS characteristics of capsular penetration have been described: tumour volume > 3 cm³; loss of normal contour of the capsule; and obliteration of the trapezoid bounded by the prostatic apex, the urethra, the rectal wall and the rectourethralis muscle. Seminal vesicle changes are more subtle and include focal alterations in the echogenicity, anterior displacement, asymmetry and loss of the “beak” where the seminal vesicle joins the ejaculatory duct (Hernandez and Smith, 1990).

Computed tomography (CT) and magnetic resonance imaging (MRI). CT scanning has performed poorly in the evaluation of local extension and lymph node metastases in prostate cancer patients. Overall accuracy in the assessment of local extension is 58–65%, and in the assessment of lymph node metastases, 0–81% (Mukamel *et al.*, 1986; Platt *et al.*, 1987; Kaye *et al.*, 1990). In 1 study, only 1 of 21 patients had improved staging over DRE with the use of CT and MRI (Mukamel *et al.*, 1986).

Determination of local extension by MRI is 64–83% accurate, which is marginally better than results by CT scanning (Bezzi *et al.*, 1988). Identification of lymph nodes is poor because of the high incidence of microscopic metastases to pelvic lymph nodes.

Prostate-specific antigen (PSA). Most of the data published about PSA show that it is nominally useful in staging prostate cancer patients. Each gram of cancer contributes approximately 3.5 ng/ml to the PSA level, while a gram of benign prostate adenoma raises PSA to 0.3 ng/ml. (Stamey *et al.*, 1989). PSA levels are highly correlated with extent of disease, capsular penetration, seminal vesicle invasion and metastases. However, cutoff levels for locally invasive or metastatic disease that accurately differentiated between these stages could not be found (Oesterling *et al.*, 1988; Lange *et al.*, 1989; Stamey *et al.*, 1989; Palken *et al.*, 1990). Others found that a PSA < 10 ng/ml was highly predictive of negative lymph nodes on examination, whereas a PSA > 50 ng/ml corresponded to a 90–100% seminal vesicle involvement rate and a 20–66% lymph node involvement rate (Stamey *et al.*, 1989; Palken *et al.*, 1990). While PSA levels are suggestive

of cancer volume and stage, categorical levels for separating tumour stages do not exist.

Prostatic acid phosphatase (PAP). Fallon and Williams (1990) reported a PAP elevation in 34–64% of patients with clinical stage C disease. A recent study by Stamey *et al.* (1989) has refuted the predictive value of PAP for invasive or metastatic disease. Of 89 patients with stage A or B disease, 20 (22%) had an elevated PAP level that would have classified their disease as stage D0; however, all patients had benign nodes at surgical staging and 3 had seminal vesical invasion. PSA was significantly more sensitive to tumour volume, local tumour extension and metastatic disease than was PAP.

DNA ploidy. The predictive value of DNA ploidy for disease recurrence was stronger than the presence of seminal vesicle invasion in one study (Lee *et al.*, 1988). The 5-year disease-free survival rate was 85% for patients with diploid tumours and 9% for those with aneuploid tumours. The predictive power of ploidy was sustained even after the effects of seminal vesicle invasion and Gleason's score were discounted.

Lymph node dissection. In stage C cancer, where 46% of patients are likely to have occult positive nodes, some clinicians have used lymph node dissections for staging disease before they initiate radiation or surgical therapy (Catalona and Scott, 1986). The accuracy of a pathological diagnosis is unsurpassed by any other modality; the morbidity of inappropriate treatment in the patient with undiagnosed metastatic disease must be weighed against that of the lymph node dissection.

When dissection was limited to the space between the external and internal iliac veins, and radical prostatectomy or radiation therapy was subsequently used, the rate of major complications was reported to be approximately 7%. Such complications included pulmonary emboli, deep venous thrombosis and nerve palsies. Minor complications occurred in 18% of the patients (Boykin and Thompson, 1990).

Treatment

The current therapy rendered to patients with clinical or pathological stage C prostate cancer runs the gamut of options available to all stages of the disease. Deciphering which treatment option is the best for individual patients is fraught with difficulty

because of the inaccuracies in clinical staging and the inability to find matched series with which to compare results. In addition, stage C disease is associated with only a 50% 5-year survival rate, and the majority of patients are eventually treated with hormonal therapy, which thus obscures survival statistics (Byar, 1973). Examination of the American College of Surgeons patterns of care study revealed a shift in the 1980s toward more radiation therapy and away from hormonal therapy alone or in combination with surgery in patients with clinical stage C prostate cancer (Schmidt *et al.*, 1986). In the 1990s, the pendulum seems to be swaying back towards combination therapy, including earlier hormonal therapy, and away from radiation therapy as a single-modality treatment.

Radiation therapy

External Beam. The rationale supporting the use of external-beam radiation therapy for disease extending beyond the confines of the capsule is that radiation fields can be changed to include locally diseased areas. Thus, radiation therapy has the potential to treat what would be considered to be beyond the margins of a surgical cure. A treatment dose beyond 6300 rads does not seem to influence either survival or local control in stage C prostate cancer.

Table 1 shows the survival and local control rates of several large series of irradiated patients. A group from the M. D. Anderson Hospital and Tumour Institute reported its treatment findings on 551 patients with clinical stage C disease who were seen between 1965 and 1982 and followed up for at least 3 years (Zagers *et al.*, 1987). There was no statistically significant survival difference when patients were evaluated according to the radiation

Table 1 External-Beam Radiation Therapy for Clinical Stage C Prostate Cancer*

Institution	Disease-free survival (%)			Local control (%)
	5 yr	10 yr	15 yr	
Mason Clinic	59	31	—	—
Mayo	77	—	—	86
Stanford	61	36	18	—
M. D. Anderson	72	47	27	75
Mallinckrodt	65	35	—	60

* Data derived respectively from Gibbons *et al.*, 1979; Zincke *et al.*, 1986; Bagshaw *et al.*, 1987; Zagers *et al.*, 1987; Lai *et al.*, 1990.

dose administered. Treatment techniques varied over the years as a matter of policy, and most patients were eventually treated with endocrine manipulation.

Results of local control rates following radiation therapy vary with the criteria used to define control. Prostate needle biopsies after radiation therapy yield positive results in 39–57% of cases. While this finding suggests a high failure rate, Gibbons *et al.* (1979) reported that only 8% (27) of 209 patients required subsequent surgery for relief of obstruction. The long-term significance of positive biopsy results in this setting is yet to be determined.

External-beam radiation therapy is tolerated fairly well. The incidence of moderate complications ranges from 9–23%, while the incidence of severe complications is approximately 6.7% (Lai *et al.*, 1990). In the M. D. Anderson study, up to 23% of patients had anal/rectal symptoms and 17% had urinary symptoms (Zagers *et al.*, 1987).

Interstitial radiation therapy. Studies evaluating interstitial radiation therapy that include long-range survival data are lacking (Table 2). The Memorial Sloan-Kettering Cancer Center reported the results of treating patients with interstitially implanted iodine 125 seeds (Whitmore *et al.*, 1985). There were 143 patients with clinical stage C cancer; during follow-up periods ranging from 2 to 10 $\geq$ years, 18% had local recurrence only, while 54% had distant metastases (with or without local disease). The 5-year survival rate was 59%. There was a distinct difference in recurrence rate between high-grade and low-grade lesions (97% and 58%, respectively), and a distinct survival difference between patients with stage C1 and C2 disease and those with C3 disease (69% and 13%, respectively). Schellhammer and El-Mahdi (1987) reported a 4%

local failure rate for stage C prostate cancer patients treated with interstitial ^{125}I seeds, which is lower than the 28% failure rate reported with external-beam radiation (Table 2). The Baylor group, using a combination of gold Au 198 interstitial therapy and external-beam radiation therapy, reported a disease-free survival of 51% at 5 years and 23% at 10 years for patients with clinical stage C disease (Carlton, 1989). This treatment was not used in patients with clinical stage C2 disease, thus making comparison difficult.

One of the perceived problems with interstitial radiation therapy has been the difficulty of accurate seed implantation to ensure the delivery of an adequate dose to the tumour burden. With improvement in ultrasound techniques, there seems to be an increasing interest in resurrecting interstitial radiation treatment by use of the perineal approach with ultrasound guidance. There are no long-term studies to assess survival, but local control continues to be a problem, with 50% positive post-treatment biopsy results reported (Loening and Kwon, 1989). The use of interstitial radiation therapy as sole treatment of clinical stage C disease does not seem to offer any advantages over external-beam radiation therapy but may benefit selected patients when it is combined with other therapies.

Transurethral resection of the prostate (TURP)

Transurethral prostatectomy has certainly been used to treat patients with clinical stage C prostate cancer, usually as palliation for symptoms caused by outlet obstruction rather than as primary therapy directed to the malignancy. Hanks *et al.* (1983) reported a significant negative impact on the survival of patients with stage C disease that was initially diagnosed by TURP rather than by needle biopsy. This series, however, does not take into account the volume of disease or the presence of symptoms. For example, do most patients who undergo TURP really have stage C2 disease, since they have significant outflow obstruction? The Mayo Clinic reported that while TURP is associated with a decrease in local control, TURP has no impact on prognosis, regardless of the tumour grade (Loening and Kwon, 1989). To address the issue of tumour spread by TURP, Paulson and Cox (1987) reported their findings on 145 patients who had undergone radical prostatectomy. Cancer diagnosis was established by TURP in 33 patients and by needle biopsy in 100. No increase in metastatic disease could be identified in group who underwent TURP before prostatectomy. Thus, the potential

Table 2 Interstitial Radiation Therapy for Clinical Stage C Prostate Cancer*

Institution		Disease-free survival (%)			Local control (%)	
		Treatment	5 yr	10 yr		15 yr
MSKCC	¹²⁵ I		59	—	—	18
Eastern Virginia	¹²⁵ I		—	—	—	44
Baylor	¹⁹⁸ Au		51	23	—	62
Iowa	Perineal		—	—	—	50

* Data derived respectively from Whitmore *et al.*, 1985; Schellhammer and El-Mahdi, 1987; Carlton, 1989; Loening and Kwon, 1989.

negative impact of TURP on survival has not been proved in this particular study.

Radical surgery

As with other modalities, it is difficult to interpret results of surgical series dealing with stage C disease because of the inclusion of other treatment modalities as adjuvant therapy. Zincke *et al.* (1986) reported on 101 patients with clinical stage C lesions who had undergone radical prostatectomy. Patients with subtrigonal involvement were excluded. Of the 101 patients, 49 had pathological stage C tumours while the remainder had ≥ 1 positive pelvic lymph nodes. Local recurrence occurred in 28% of patients who had no adjuvant treatment but not in any patients who had an orchiectomy. Orchiectomy, however, had no effect on survival. The observed survival rate at 5 and 10 years was similar to that of age-matched controls. Survival rates will improve or change significantly only if surgery can remove all tumour. Bosch *et al.* (1987) reported that only 14 (29%) of 48 patients in their series had complete tumour removal as defined by negative lymph nodes and negative margins of resection.

Local failure or recurrence rates associated with radical prostatectomy have varied, with 8.7% reported by Tomlinson *et al.* (1977) and 28% reported by Zincke *et al.* (1986) in those patients not receiving adjuvant therapy.

Several reports have addressed the issue of more extensive surgical procedures for clinical stage C disease. Spaulding and Whitmore (1978) reported on 37 patients managed by pelvic exenteration or cystoprostatectomy. Local control for stage C lesions was 48%. Of the 35 patients who survived the surgery, 24 died of prostate cancer; only 7 survived 9–20 years with no further evidence of disease. Two patients died after surgery and 19 experienced complications. Many of these patients had some form of therapy before surgery. Moul and Paulson (1990) reported on 22 patients who underwent salvage surgery. Ten of the 22 patients had no previous therapy; of this subgroup, 9 were alive at 59 months and 3 had negative surgical margins. The other 12 patients in the series had surgery for radiorecurrent disease.

Hormonal therapy

The Veterans Administration Cooperative Urological Research Group (VACURG) studies are the only significant studies dealing with hormonal therapy alone in patients with stage C disease

(Byar, 1973). These studies have demonstrated that although there is certainly a delay in progression to stage D2 disease (15% at 5 years and 25% at 10 years with hormonal therapy, versus 40% at 5 years and 60% at 10 years with placebo), there does not appear to be a survival advantage.

A growing interest in the use of hormonal therapy to treat clinical stage C disease has been fuelled by the significant percentage of failures with other treatments. The NCI study on complete androgen blockade in the treatment of advanced-stage prostate cancer suggests that total androgen blockade may prolong survival (Crawford *et al.*, 1989). In terms of local control, Fleischman and Catalona (1985) reported that 68% of patients treated with hormonal therapy (orchiectomy) had resolution of obstructive symptoms without requiring further local control.

Combination therapy

The enthusiasm for post-radiation radical prostatectomy or cystoprostatectomy for radiorecurrent disease is waning as the role of prostatectomy appears to be expanding. Zincke (1990) reported on 62 patients who had undergone salvage surgery after radiation failure. Overall survival was 65% at 5 years and 41% at 10 years. He concluded that radical prostatectomy may have a role after radiation failure in small-volume disease but that the wisdom of exenterative procedures for large-volume disease seems questionable, except for local palliative control. In Moul and Paulson's series of 12 patients, disease was confined to the surgical specimen in 41.7% (Moul and Paulson, 1990). Goldstone and Scardino (1990) reported that 41% of their series of 28 patients had negative surgical margins and no seminal vesicle invasion. Rectal injuries occurred in 18% and anastomotic strictures in 21%. Complete urinary continence was achieved in only 60%. Thus, although it may be possible to surgically excise all tumour and recurrent disease related to radiation therapy, the complication rate is certainly higher; therefore, the clinician must be selective about the indications for such procedures. Gill *et al.* (1980) reported on "sandwich" radiation therapy, in which 15 patients with clinical stage C prostate cancer were treated with 3000 rads, underwent radical prostatectomy, and then received an additional 2000 rads to the pelvis, 2500 rads to the prostatic fossa and 4500 rads to the periaortic-cava lymph node area. Recuperative periods followed the initial dose and the prostatectomy. These patients had no demonstrable local recurrence of

disease in the pelvis, but follow-up was only 6 months to 5.5 years.

Perhaps the most commonly used combination therapy at present is that of radical prostatectomy followed by external-beam radiation therapy. It must be remembered that such therapy is typically reserved for patients thought to have organ-confined disease but who, on pathological examination of excised specimens, are found to have positive surgical margins, seminal vesicle involvement, or confirmed organ-positive, surgical margin-negative disease. Post-prostatectomy radiation therapy can reduce PSA levels in 82% of patients and can normally reduce local recurrences in the 5–28% range, but there is no confirmed data suggesting a survival advantage (Lange *et al.*, 1990).

Another combination treatment generating widespread interest, although proof of its efficacy is lacking, is pre-operatively administered hormonal therapy to “downstage” stage B2 and C disease. Scott and Boyd reported on this concept in 1969. In their series of 39 selected patients, the overall 5-year survival rate was 74.4% with 61.5% being disease-free. Thirty-three patients followed up for 10 years showed a 51.5% disease-free survival rate. The Radiation Therapy Oncology Group (RTOG) conducted a randomised trial from 1983 to 1986, randomising patients to receive either megestrol or diethylstilbestrol (DES) followed by radiation therapy. Their study showed no advantage for either drug (Pilepich *et al.*, 1989).

Soloway (1990) is currently studying a group of 20 patients treated for several months with pre-operatively administered hormonal therapy constituting luteinising hormone-releasing hormone (LHRH) agents and flutamide. Three of 20 patients had positive nodes, and 9 of 20 had margin-positive disease. Six patients have had continuation of androgen deprivation therapy. Although a 30–50% reduction in tumour size is possible, there is no definitive evidence of eventual confinement of disease to the organ.

Thompson *et al.* (1991) recently reported on a group of 24 patients with histological or imaging evidence of extracapsular or seminal vesical disease. Eighteen were treated with a combination of an LHRH agonist and flutamide, 4 with an LHRH agonist alone, and 2 with DES. All patients were treated for 3 months. Although 70% were clinically downstaged, 35% had positive nodes confirmed at the time of node dissection and 80% had extracapsular disease at the time of surgery. Of the 3 patients with organ-confined disease, 2 had pre-operative findings suggestive of seminal vesicle invasion and

1 had a rising PSA level. Therefore, to date there is no scientific data to support the use of pre-operatively administered hormonal therapy to pathologically downstage patients with locally advanced disease.

References

- Andriole, G. L., Kavouni, L. R., Torrence, R. J. *et al.* (1988). Transrectal ultrasonography in the diagnosis and staging of carcinoma of the prostate. *J. Urol.*, **140**, 758–760.
- Bagshaw, M. A., Ray, G. R. and Cox, R. S. (1987). Selecting initial therapy for prostate cancer: radiation therapy perspective. *Cancer*, **60**, 521–525.
- Bezzi, M., Kressel, H. Y., Allen, K. S. *et al.* (1988). Prostatic carcinoma. staging with MR imaging at 1.5 T1. *Radiology*, **169**, 339–346.
- Bosch, R. J. L., Kurth, K. H. and Schroeder, F. H. (1987). Surgical treatment of locally advanced (T3) prostatic carcinoma: early results. *J. Urol.*, **138**, 816–822.
- Boykin, W. H., Jr. and Thompson, I. M., Jr. (1990). Morbidity of modified pelvic lymphadenectomy: review of 139 cases. *AUA Abstract No. 893*
- Byar, D. P. (1973). The Veterans Administration Cooperative Urological Research Group's studies of cancer of the prostate. *Cancer*, **32**, 1126–1130.
- Carlton, C. E., Jr. (1989). Combined interstitial and external irradiation in the definitive treatment of localized prostatic cancer. In *Controversies in Urology*, ed. Carlton, C. E., Jr. Chapter 22B, pp. 276–280. Chicago: Year Book Medical Publishers.
- Catalona, W. J. and Scott, W. W. (1986). Carcinoma of the prostate. In *Campbell's Urology*, ed. Walsh, P. C., Gittes, R. F., Perlmutter, A. D., *et al.* Fifth edition. Chapter 32, pp. 1463–1534. Philadelphia: Saunders.
- Catalona, W. J. and Stein, A. J. (1982). Staging errors in clinically localized prostatic cancer. *J. Urol.*, **127**, 452–456.
- Crawford, E. D., Eisenberger, M. A., McLeod, D. G. *et al.* (1989). A controlled trial of leuprolide with and without flutamide in prostatic carcinoma. *N. Engl. J. Med.*, **321**, 419–424.
- Fallon, B. and Williams, R. D. (1990). Current options in the management of clinical stage C prostatic carcinoma. *Urol. Clin. North Am.*, **17**, 853–866.
- Fleischman, J. D. and Catalona, W. J. (1985). Endocrine therapy for bladder outlet obstruction from carcinoma of the prostate. *J. Urol.*, **134**, 498–500.
- Gibbons, R. P., Mason, J. T., Correa, R. J., Jr. *et al.* (1979). Carcinoma of the prostate: local control with external beam radiation therapy. *J. Urol.*, **121**, 310–312.
- Gill, W. B., Schoenberg, H. W., Banno, J. J. *et al.* (1980). Sandwich radiotherapy (3,000 and 4,000 rads) around radical retropubic prostatectomy for stage C prostatic carcinoma. *Urology*, **16**, 470–475.
- Goldstone, L. M. and Scardino, P. T. (1990). Salvage radical prostatectomy in radiorecurrent adenocarcinoma of the prostate. *AUA Abstract No. 126*.
- Hanks, G. E., Leibel, S. and Kramer, S. (1983). The dissemination of cancer by transurethral resection of locally advanced prostate cancer. *J. Urol.*, **129**, 309–311.
- Hernandez, A. D. and Smith, J. A., Jr. (1990). Transrectal ultrasonography for the early detection and staging of prostate cancer. *Urol. Clin. North Am.*, **17**, 745–757.
- Johansson, J.-E., Adami, H.-O., Andersson, S.-O. *et al.* (1992). High 10-year survival rate in patients with early, untreated prostatic cancer. *J.A.M.A.*, **267**, 2191–2196.

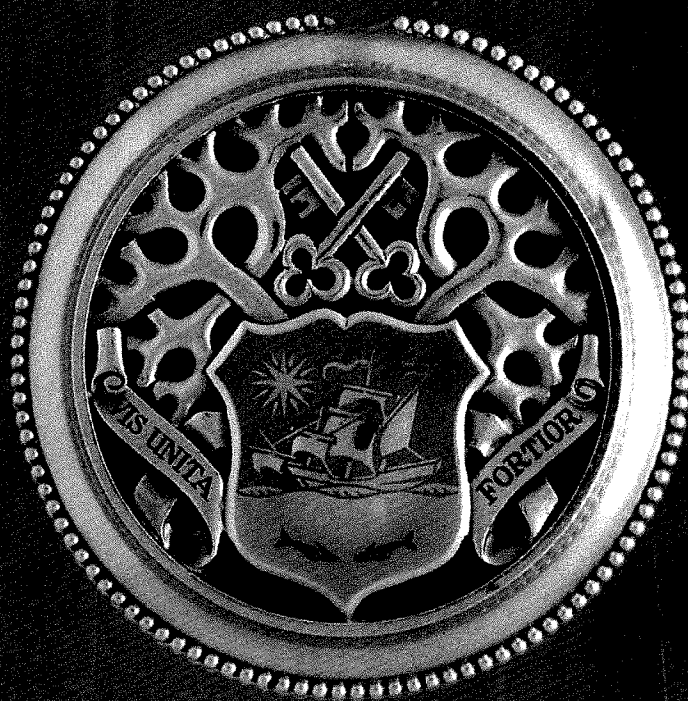
- Kaye, R. I., Paul-Blanc, R., Wilbur, H. J. *et al.* (1990). Value of abdominopelvic CT scanning in treatment planning of prostate cancer. *AUA Abstract* No. 77.
- Lai, P. P., Perez, C. A., Shapiro, S. J. *et al.* (1990). Carcinoma of the prostate stage B and C: lack of influence of duration of radiotherapy on tumor control and treatment morbidity. *Int. J. Radiat. Oncol. Biol. Phys.*, **19**, 561–568.
- Lange, P. H., Ercole, C. J., Lightner, D. J. *et al.* (1989). The value of serum prostate specific antigen determinations before and after radical prostatectomy. *J. Urol.*, **141**, 873–879.
- Lange, P. H., Lightner, D. J., Medini, E. *et al.* (1990). The effect of radiation therapy after radical prostatectomy in patients with elevated prostate specific antigen levels. *J. Urol.*, **144**, 927–933.
- Lange, P. H. and Narayan, P. (1983). Understaging and undergrading of prostate cancer: argument for postoperative radiation as adjuvant therapy. *Urology*, **21**, 113–118.
- Lee, S. E., Currin, S. M., Paulson, D. F. *et al.* (1988). Flow cytometric determination of ploidy in prostatic adenocarcinoma: a comparison with seminal vesicle involvement and histopathological grading as a predictor of clinical recurrence. *J. Urol.*, **140**, 769–774.
- Loening, S. A. and Kwon, E. D. (1989). Percutaneous transperineal placement of radioactive gold seeds for treatment of localized prostatic carcinoma. *J. Endourol.*, **3**, 201.
- McNeal, J. E., Bostwick, D. G., Klindschuk, R. A. *et al.* (1986). Patterns of progression in prostate cancer. *Lancet*, **1**, 60–63.
- Moul, J. W. and Paulson, D. F. (1990). The role of radical surgery in the management of large volume T3 and T4 and radiation persistent cancer. *AUA Abstract* No. 122.
- Mukamel, E., deKernion, J. B., Dorey, F. *et al.* (1990). Significance of histological prognostic indicators in patients with carcinoma of the prostate. *Br. J. Urol.*, **65**, 46–50.
- Mukamel, E., Hannah, J., Barbaric, Z. *et al.* (1986). The value of computerized tomography scan and magnetic resonance imaging in staging prostatic carcinoma: comparison with the clinical and histological staging. *J. Urol.*, **136**, 1231–1233.
- Oesterling, J. E., Chan, D. W., Epstein, J. I. *et al.* (1988). Prostate specific antigen in the preoperative and postoperative evaluation of localized prostatic cancer treated with radical prostatectomy. *J. Urol.*, **139**, 766–772.
- Palken, M., Cobb, O. E., Warren, B. H. *et al.* (1990). Prostate cancer: correlation of digital rectal examination, transrectal ultrasound and prostate specific antigen levels with tumour volumes in radical prostatectomy specimens. *J. Urol.*, **143**, 1155–1162.
- Paulson, D. F. and Cox, E. B. (1987). Does transurethral resection of the prostate promote metastatic disease? *J. Urol.*, **138**, 90–91.
- Perrapato, S. D., Carothers, G. C., Maatman, T. J. *et al.* (1989). Comparing clinical staging plus transrectal ultrasound with surgical-pathologic staging of prostate cancer. *Urology*, **33**, 103–105.
- Pilepich, M. V., Krall, J. M., John, M. J. *et al.* (1989). Hormonal cytoreduction in locally advanced carcinoma of the prostate treated with definitive radiotherapy: preliminary results of RTOG 83–07. *Int. J. Radiat. Oncol. Biol. Phys.*, **16**, 813–817.
- Platt, J. F., Bree, R. L. and Schwab, R. E. (1987). The accuracy of CT in the staging of carcinoma of the prostate. *AJR*, **149**, 315–318.
- Schellhammer, P. F. and El-Mahdi, A. M. (1987). Prostate biopsy after definitive treatment by interstitial ¹²⁵Iodine implant or external beam radiation therapy. *J. Urol.*, **137**, 897–901.
- Schmidt, J. D., Mettlin, C. J., Natarajan, N. *et al.* (1986). Trends in patterns of care for prostatic cancer, 1974–1983: results of surveys by the American College of Surgeons. *J. Urol.*, **136**, 416–421.
- Scott, W. W. and Boyd, H. C. (1969). Combination hormone control therapy and radical prostatectomy in the treatment of selected cases of advanced carcinoma of the prostate: a retrospective study based upon 25 years of experience. *J. Urol.*, **101**, 86–92.
- Soloway, M. S. (1990). Androgen deprivation prior to radical prostatectomy. Presented at Progress Report on the Clinical Treatment of Prostatic Cancer; Dec. 6–9, 1990; Scottsdale, Arizona, U.S.A.
- Spaulding, J. T. and Whitmore, W. F., Jr. (1978). Extended total excision of prostatic adenocarcinoma. *J. Urol.*, **120**, 188–190.
- Stamey, T. A., Kabalin, J. N., McNeal, J. E. *et al.* (1989). Prostate specific antigen in the diagnosis and treatment of adenocarcinoma of the prostate. II. Radical prostatectomy treated patients. *J. Urol.*, **141**, 1076–1083.
- Stamey, T. A., Villers, A. A., McNeal, J. E. *et al.* (1990). Positive surgical margins at radical prostatectomy: importance of apical dissection. *J. Urol.*, **143**, 1166–1173.
- Thompson, I. M., Lowe, B. A., Carroll, P. R. *et al.* (1991). A multicenter study of hormonal “downstaging” of clinical stage C carcinoma of the prostate followed by radical prostatectomy. *AUA Abstract* No. 413.
- Tomlinson, R. L., Currie, D. P. and Boyce, W. H. (1977). Radical prostatectomy: palliation for stage C carcinoma of the prostate. *J. Urol.*, **117**, 85–87.
- Villers, A. A., McNeal, J. E., Redwine, E. A. *et al.* (1990). Pathogenesis and biological significance of seminal vesicle invasion in prostatic adenocarcinoma. *J. Urol.*, **143**, 1183–1187.
- Whitmore, W. F., Jr., Hillaris, B., Batata, M. *et al.* (1985). Interstitial radiation: short-term palliation or curative therapy? *Urology*, **25**(Suppl), 24–29.
- Zagers, G. K., von Eschenbach, A. C., Johnson, D. E. *et al.* (1987). Stage C adenocarcinoma of the prostate: an analysis of 551 patients treated with external beam radiation. *Cancer*, **60**, 1489–1499.
- Zhucke, H. (1990). Radical prostatectomy (RP) and exenterative procedures (EX) for local failure following radiotherapy with curative intent: A comparison in disease outcome. *AUA Abstract* No. 124.
- Zhucke, H., Utz, D. C. and Taylor W. F. (1986). Bilateral pelvic lymphadenectomy and radical prostatectomy for clinical stage C prostatic cancer: role of adjuvant treatment for residual cancer and in disease progression. *J. Urol.*, **135**, 1199–1205.

The Authors

J. H. Lynch, MD, Chief of Division of Urology.
C. W. Graham, MD, Resident.

Requests for reprints to: J. Lynch, Division of Urology, Georgetown University Hospital, 3800 Reservoir Road N.W., Washington, DC 20007, USA.

British Journal of UROLOGY



CHURCHILL LIVINGSTONE

Rec 12 ¹¹/₉₂

BRITISH JOURNAL OF UROLOGY

Journal of the
British Association of Urological Surgeons
and the European Society of Paediatric Urology

Editor

*G. D. CHISHOLM

Honorary Treasurer

*J. P. PRYOR

Editorial Assistant

EDNA MacDONALD

Assistant Editors

R. J. MILLARD

*J. E. NEWSAM

*R. H. WHITAKER

Editorial Committee

Chairman J. H. STEYN*

E. P. ARNOLD, Christchurch
M. HANDLEY ASHKEN, Norwich
M. BHANDARI, Lucknow
*M. C. BISHOP, Nottingham
*J. P. BLANDY, London
A. C. BUCK, Glasgow
C. A. C. CHARLTON, Bath
D. J. DU PLESSIS, Pretoria
*J. M. FITZPATRICK, Dublin
J. C. GINGELL, Bristol
J. A. GOSLING, Hong Kong
*R. R. HALL, Newcastle upon Tyne
T. B. HARGREAVE, Edinburgh
*†K. HJÄLMÅS, Gothenburg
W. F. HENDRY, London
D. KIRK, Glasgow
V. R. MARSHALL, Adelaide

*A. R. MUNDY, London
D. E. NEAL, Newcastle upon Tyne
P. H. O'REILLY, Stockport
K. F. PARSONS, Liverpool
W. B. PEELING, Newport
A. RIZVI, Karachi
*R. J. MORGAN, London
†H. J. F. R. SERUCA, Lisbon
T. SHERWOOD, Cambridge
F. P. SOONAWALLA, Bombay
D. F. M. THOMAS, Leeds
H. N. WHITFIELD, London
J. E. A. WICKHAM, London
GORDON WILLIAMS, London
*R. E. WILLIAMS, Leeds
C. R. J. WOODHOUSE, London
P. H. L. WORTH, London

*Member of Executive Committee

†Member of E.S.P.U.

Former Editors

H. P. WINSBURY-WHITE, 1929-1948
D. BAND, 1949-1966
J. D. FERGUSSON, 1967-1972
W. KEITH YEATES, 1973-1977

Churchill Livingstone 

Instructions to Authors

The *British Journal of Urology* welcomes original contributions on urological subjects from all parts of the world. Papers are accepted for consideration on the understanding that their contents have not been published in whole or in part elsewhere, that they are subject to editorial revision, and that the Editor is responsible for the order of publication. Papers on nephrology, of interest to the urological surgeon, are welcome. When relevant, authors must include a statement on the ethical aspects of their research.

Manuscripts. Papers should be submitted in Journal style. Failure to do so may lead to significant delays in publication. Papers should be typewritten in double spacing on A4 paper (21 × 29.7 cm) with a margin of at least 3 cm all round. Two copies of the manuscript and illustrations should be submitted and the author should retain a copy for reference.

Authorship. All authors must give signed consent to publication. Only those who have made a substantial contribution to the work should be designated as authors and a maximum number of five is preferred. Those who have made a smaller contribution should be recognised separately in the Acknowledgements section.

Original articles should be set out as follows, with each section beginning on a separate page: title page, summary, text, references, authors' page, tables, legends to illustrations.

The *title page* should give the following information: (1) title of article, (2) initials and names of each author; (3) the department and institution to which the work should be attributed.

The *summary* should consist of very brief statements about each of the main sections.

A list of 3 to 6 *key words* should be provided.

The *text* should be arranged as follows: (1) Introduction, (2) Patients and Methods, or Materials and Methods; (3) Results, (4) Discussion and Conclusions, (5) Acknowledgements.

References. The author is responsible for the accuracy of his references. When quoted in the text they should include the author's name and year of publication. In the case of 2 authors both names should be cited. If there are more than 2 authors, only the first author plus *et al.* should be quoted. The list of references at the end of the paper should be in alphabetical order and should give the names of *all* authors unless there are more than three, when only the first three should be given followed by *et al.* With journal references the following sequence should be observed: name(s); initials; date; title of paper, name of journal abbreviated according to *Index Medicus*; volume number; first and last page numbers. Thus:

Morris, J. A., Oates, K. and Staff, W. G. (1986). Scanning electron microscopy of adenomatoid tumours. *Br. J. Urol.*, 58, 183–187.

References to books should be as follows:

Wright, F. S. and Howards, S. S. (1981). Obstructive injury. In *The Kidney*, ed. Brenner, B. M. and Rector, F. C. Second edition. Volume II. Chapter 38, pp. 2009–2044. Philadelphia: Saunders.

The *authors' page* should give the names of all authors, their qualifications and main appointment. Please indicate the name and address of the author to whom offprint requests should be made.

Tables should be kept to a minimum and laid out as simply as possible. Each should be typed on a separate sheet, numbered in Arabic numerals and should not duplicate information in the text.

Illustrations. Photographs and radiographs should be submitted in the form of half-plate prints (approximately 17 × 11 cm). All figures should be unmounted. The number of the illustration (in Arabic numerals), the author's names, and the "top" of the illustration should be indicated lightly in pencil on the back. The magnification of photomicrographs and details of staining techniques should be given. Lettering on figures must be indicated on a transparent overlay. Illustrations in colour cannot be accepted unless the author is willing to cover the cost.

Points of Technique and Case Reports should not exceed 250 words, 2 illustrations and 3 references. In **Case Reports** the sections should be (1) Case Report, (2) Comment; (3) References.

Proprietary names of drugs, instruments, etc., should be indicated by the use of initial capital letters.

Abbreviations and units. All measurements should be expressed in S.I. units except blood pressure which will continue to be expressed in mmHg. For more detailed recommendations authors may consult the Royal Society of Medicine publication entitled *Units, Symbols and Abbreviations: A guide for Biological and Medical Editors and Authors*.

Correspondence. Questions or comments concerning recently published papers may be sent to the Editor, who will refer them to the authors. The readers' comments and authors' replies may subsequently be published together in the Correspondence column.

Address. All editorial communications, including books for review, should be addressed to the Editor, Professor G. D. Chisholm, Western General Hospital, Edinburgh EH4 2XU.

Offprints. Twenty-five free offprints are supplied to the author to whom offprint requests are to be made. Order forms will be sent with the proofs for correction, all of which should be returned to the publishers within 7 days of receipt.

Subscriptions. The journal is published monthly by Churchill Livingstone. Institutional rate for 1992 is £90.00 (UK), £100.00 (overseas) or \$180.00 (USA); the Trainee rate is £39.00 (UK), £42.50 (overseas) or \$76.50 (USA) per annum, post free, for non members. Second class postage is paid at Rahway NJ Postmaster: send USA address corrections to British Journal of Urology, c/o Mercury Airfreight International Ltd Inc, 2323 Randolph Avenue, Avenel, New Jersey 07001.

This journal is indexed, abstracted and/or published on line in the following media: Adonis, Colleague (online), Current Awareness in Biological Sciences, Current Contents, Excerpta Medica, Biological Abstracts, UMI (Microfilms), BRS Colleague (full text), British Medicine, Chemical Abstracts, Modern Medicine, Index Medicus, NMLUIS Reference Up Date and UMI (Disk).

Subscription enquiries: Longman Group U.K. Limited, Subscriptions (Journals) Department, P.O. Box 77, Fourth Avenue, Harlow, Essex CM19 5BQ. Telephone 0279 623760.

Note to Users in the USA. Authorisation to photocopy items for internal or personal use is granted by the copyright holder provided that the fee of \$2 per copy plus \$1.50 per page is paid directly to Copyright Clearance Center, 27 Congress Street, Salem, MA 01970, USA. For more information, please contact CCC. For territories outside North America, permission should be sought direct from the copyright holder. This consent does not extend to other kinds of copying, such as copying for general distribution, for advertising and promotional purposes, for creating new collective works, or for resale.

0007-1331/92/\$2 per copy \$1.50 per page

Copyright © 1992 British Journal of Urology. All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, without the prior permission of the copyright owner, or a licence permitting restricted copying in the United Kingdom issued by the Copyright Licensing Agency Ltd, 90 Tottenham Court Road, London W1P 9HE.

Printed on acid-free Fineblade Smooth 100 gsm paper. The publisher's policy is to use paper manufactured from sustainable forests.

British Journal of Urology

Volume 70 No 1 Pages 1-112

July 1992

Contents

Review

Undescended Testis—the Need for a Standard Classification

R. H. Whitaker

1

Original Articles

Selective Renal Tumour Biopsy under Ultrasonic Guidance

M. Abe and M. Saitoh

7

Effect of Vaginal Ultrasound Probe on Lower Urinary Tract Function

B. G. Wise, G. Burton, A. Cutner and Linda D. Cardozo

12

Detrusor Mast Cells in Refractory Idiopathic Instability

Kate H. Moore, P. Nickson, D. H. Richmond, J. R. Sutherst, P. R. Manasse and T. R. Helliwell

17

Electromyographic Abnormalities in the Urethral and Anal Sphincters of Women with Idiopathic Retention of Urine

R. J. Webb, P. R. W. Fawcett and D. E. Neal

22

Continent Urinary Diversion Using an Artificial Urinary Sphincter

P. Mitrofanoff, O. Bonnet, M. P. Annoot, F. Bawab and P. Grise

26

The Effect of Ranitidine on Urine Mucus Concentration in Patients with Enterocystoplasty

V. K. George, J. M. Gee, M. I. Wortley, M. Stott, C. G. C. Gaches and M. H. Ashken

30

Male and Female Sexual Function and Activity Following Ileal Conduit Urinary Diversion

G. M. Nordström and C. R. Nyman

33

Cystoprostatectomy and Substitution Cystoplasty for Locally Invasive Bladder Cancer

P. J. Thomas, Diane E. Nurse, C. Deliveliotis and A. R. Mundy

40

Survey of Urological Centres and Review of Current Practice in the Pre-operative Assessment of Prostatism

A. G. Wilkinson and S. R. Wild

43

Bladder Cancer Mortality in the Netherlands, 1955-88

L. A. L. M. Kiemeny, A. L. M. Verbeek, P. J. Nelemans, J. A. Witjes and H. Straatman

46

Is Pre-operative Imaging of the Urinary Tract Worthwhile in the Assessment of Prostatism?

A. G. Wilkinson and S. R. Wild

53

Urinary Flow Rates in Patients with Benign Prostatic Hypertrophy following Treatment with Alfuzosin

P. Teillac, M. C. Delauche-Cavallier, P. Attali and the DUALF Group

58

Finasteride in the Treatment of Benign Prostatic Hyperplasia. A Urodynamic Evaluation

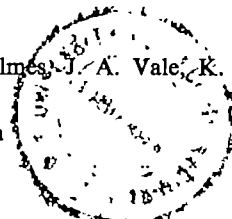
R. S. Kirby, Jenny Bryan, I. Eardley, T. J. Christmas, S. Liu, S. A. V. Holmes, J. A. Vale, K. Shanmuganathan and Judith A. Webb

65

Long-term Results of Treatment of Urethral Injuries in Males Caused by External Trauma

B. J. Jenkins, D. F. Badenoch, C. G. Fowler and J. P. Blandy

73



Treatment of Hydrocele: Randomised Prospective Study of Simple Aspiration and Sclerotherapy with Tetracycline G. Breda, A. Giunta, L. Gherardi, D. Xausa, P. Silvestre and A. Tamai.	76
New Approach to the Management of Fournier's Gangrene C. A. Attah	78
Vacuum Constriction Devices: Second-line Conservative Treatment for Impotence H. W. Gilbert and J. C. Gingell	81
Paediatric Urology	
Ten-year Review of Treatment of the Undescended Testis in the West of Ireland M. V. McKiernan, P. D. Murphy and J. G. Johnston	84
Surgical Outcome of Orchiopexy. I. Previously Unoperated Testes K. C. Saw, I. Eardley, M. J. S. Dennis and R. H. Whitaker	90
Case Reports	
Occupational Urothelial Cancer in a Former Iron Foundry Worker N. P. Cohen and D. M. Thomas	95
Malignant Hypertension due to Embolisation of a Clear Cell Renal Carcinoma C. S. J. Probert, D. E. Osborn and E. M. Watkin	95
Verrucous Carcinoma of the Bladder A. E. Groeneveld	96
Late Metastasis from Ovarian Tumour. An Unusual Cause of Hydronephrosis W. A. McCallion, P. F. Keane, B. G. Wilson and W. G. Loughridge	97
Columnar Metaplasia Complicating Neurogenic Bladder in a Child G. G. Youngson, R. Galley and P. W. Johnston	98
Syphilis of the Ureter D. J. Warwick and S. C. W. Harrison	99
Pontine Pathology and Voiding Dysfunction C. D. Betts, R. Kapoor and C. J. Fowler	100
Metastatic Carcinoid Tumour Involving the Prostate N. J. Parr, K. M. Grigor and A. W. S. Ritchie	103
Points of Technique	
Laparoscopic Excision of an Intra-abdominal Testis R. O. Beck, P. Nicholl, N. C. Hickey and J. Black	105
Use of the Lachrymal Duct Probe in Epididymal Aspiration K. R. Loughlin	106
Notices	107
Erratum Volume 69 No 2 February 1992 pages 113-120 Diuresis Renography. Recent Advances and Recommended Protocols D. H. O'Reilly	107
Diary	108
Book Reviews	110

REVIEW

Undescended Testis—the Need for a Standard Classification

R. H. WHITAKER

Department of Paediatrics, Addenbrooke's Hospital, Cambridge

Almost all of the current controversies concerning the undescended testis are caused by a lack of long-term follow-up studies and an apparent disagreement as to what constitutes an undescended testis. The 2 most obvious controversies are first, the extent to which orchiopexy helps fertility and second, the risk of malignancy in the undescended testis. Statistics produced over many years are confusing, particularly because they differ so widely between observers, but also because they are not based on a standard or accepted classification of the anomaly.

The Need for a Classification

Several attempts at classifying undescended testes have been made (Schoorl, 1982; Beltran-Brown and Villegas-Alvarez, 1988; Moul and Belman, 1988) but none has provided the clinician with a comprehensive, simple and practical guide that everyone could accept. The main reason for the failure to produce an adequate classification is that it has not been appreciated that there are 3 separate ways of considering the position of the testis. It can be categorised (1) after a simple palpation, (2) after manipulation of the testis to its optimum or lowest position or (3) according to the position in which it is found at surgery (Table 1). An obvious example of this confusion is the boy whose testis is initially impalpable but after careful examination it can be stroked out of the inguinal canal to an emergent position. At the time of surgery, however, the testis is lying in a large sac just inside the internal ring in the abdomen. Is this an abdominal, canalicular or an emergent testis? Another example is the testis

that spends most of its time in the superficial inguinal pouch but can be manipulated to a high scrotal position and then retracts back into the superficial pouch when it is released. It is clearly retractable but is it basically ectopic or high scrotal?

A classification is proposed that takes all 3 of these ways of designating the position of the testis into account (Table 2). It has certain criteria which are as follows:

1. The position for classification in a palpable testis is the lowest position into which the testis can be comfortably manipulated without tension. In an impalpable testis it is the lowest position in which the testis lies when it is first exposed at operation.
2. Any testis, normally descended or undescended, can be retractile provided that it is beyond the

Table 1 Criteria for Classification

1. Position at simple palpation
2. Position after manipulation to lowest position
3. Position at surgical exploration

Table 2 Proposed Classification

Impalpable	Modified at operation to
	Absent
	Abdominal
	Canalicular
Palpable	Emergent
	Superficial inguinal pouch (can be manipulated into the scrotal neck)
	High or mid-scrotal
	Ectopic (see text for positions but if it is in the superficial inguinal pouch it cannot be manipulated into the scrotal neck)

Note: All palpable testes, including normal ones, can be retractile.

external ring. Retractility is not, *per se*, part of the classification of undescended testis but simply an adjective to be added, as necessary, to the position of any palpable testis.

3. Any testis that lies at rest in the normal pathway of descent, or can be manipulated into it, is a truly undescended testis. This includes the vast majority of testes in the superficial inguinal pouch that can be manipulated into the upper scrotum.
4. Conversely, any testis that cannot be manipulated to the normal path of descent is ectopic. This includes the classically described, but rarely seen, examples of testes in the upper thigh, perineum or base of penis. More importantly, however, it also includes those not so uncommon examples of testes in the superficial inguinal pouch that cannot be manipulated out of the pouch either back into the canal or down into the scrotum. This group will be mentioned again later.

Suggested Classification

1. Impalpable

Any testis that is not palpable can be canalicular (within the inguinal canal), abdominal or absent. Approximately 5% of all impalpable testes are absent. The final position of an impalpable testis is only discovered at surgical exploration, at which time the pre-operative designation of impalpable can be modified to one of the above.

2. Palpable

(a) Emergent. A few testes lie at rest just outside the external ring in the normal pathway of descent. Others can be manipulated to this position.

(b) Superficial inguinal pouch. This is the most common position in which to find an undescended testis. It has emerged from the external ring and has passed superficial to the external oblique muscle to a subcutaneous position. Such a testis is usually very mobile and provided that it can be manipulated down into the neck or upper part of the scrotum, it should be considered as a truly undescended testis and not ectopic. Occasionally such a testis in the superficial inguinal pouch can be pushed back into the canal. As mentioned earlier, a few testes in the superficial inguinal pouch cannot be manipulated into the scrotum and these are ectopic. The reason is perfectly clear at the time of orchiopexy when a hammock of fibrous tissue is found across the neck of the scrotum which needs to be broken down by a finger to gain access into the scrotum. We would

stress that only when a testis in the superficial inguinal pouch is obstructed in this way can it be called ectopic.

(c) High scrotal and mid-scrotal. Many testes can be manipulated to a high or mid-scrotal position, although most of these will retract to an even higher position on being released. Most observers would agree that a high scrotal testis is not good enough and that an orchiopexy is needed. A mid-scrotal testis is more controversial. Indeed, there is only a subtle difference between a mid-scrotal and an asymmetrically lying normal one. The need for surgery versus observation is debatable. Reassurance is probably not good enough in a young child as it is our contention that many, or possibly most ascending testes (Atwell, 1985) originate from this group of mid-scrotal testes.

An increasing awareness of these high or mid-scrotal testes may be amongst the reasons for the apparent doubling in the rate of orchiopexy that has been reported (Chivers *et al.*, 1984). Both of these types of testis are usually quite retractable, so that before manipulation they may be in an emergent or superficial inguinal pouch position. A steady but gentle traction may be necessary to determine their final position for this classification.

(d) Ectopic. There are numerous case reports of testes being found in positions that are clearly away from the normal path of descent, such as on the abdominal wall, in the upper thigh, in the perineum or at the base of the penis. There is no doubt that these are ectopic. To this group we add the testis, mentioned above, that lies in the superficial inguinal pouch but cannot be manipulated into the upper scrotum. We appreciate that this is somewhat controversial but it has important implications, for example, for the success or otherwise of hormonal treatment for undescend. These ectopic (obstructed) testes have a good length of cord and can be brought down easily by operation but, though palpable, could never descend under the influence of hormone treatment (Karpe *et al.*, 1983).

Retractility. The problem of excluding retractility has been the most potent cause of confusion in interpreting the statistics and deciding on the best clinical management. Between a quarter and a third of all boys referred to clinics with suspected undescended testes are found to have normal, albeit retractile testes (Cour-Palais, 1966; Whitaker, 1970; Rajfer *et al.*, 1986). If this problem of excluding retractility leads the surgeon to over-diagnose the number of undescended testes, then this may be yet another factor in the apparent

doubling of the rate of orchiopexy in recent years (Chivers *et al.*, 1984). If the testis is normal but simply retractile it will come to rest at the bottom of the scrotum at puberty and there is no convincing evidence that it will come to any harm from its temporary rest in the inguinal region. For all we know, retractile testes may only be retracted during the periods of observation and for the rest of the day and night they may be well into the scrotum!

It is beyond the scope of this discussion to describe in detail the examination of boys for undescended testis but suffice it to say that if the inside of the ipsilateral leg is gently stroked with the tip of a finger a retractile testis can be seen to move even if it is in the superficial inguinal pouch. A stroking action of the fingers downwards over the region of the canal and superficial inguinal pouch will coax many testes into the neck of the scrotum, where they can then be grasped by the fingers of the other hand and manipulated to their lowest position (Whitaker, 1990).

Such examination techniques are probably of paramount importance, since inter-observer variation may well account for sources of bias between series (Olsen, 1989).

Thus this simple classification provides a description of all of the categories of undescend that are encountered provided that the opportunity is taken to feed into it the combined findings at first examination, after palpation and manipulation, and at the time of initial exposure at operation.

Effect of Classification on Hormone Treatment

So many reports have extolled the virtues of GnRH and HCG treatment for undescended testes that it is now difficult to refute the success of such treatment in selected cases. It would be oversimplistic to suggest that good results are seen primarily in retractile testes (Rajfer *et al.*, 1986), but the variability of results from 5 to 80% makes one wonder if retractility, and the inability of some workers to exclude it, is a powerful factor in this wide inconsistency.

Effect on Infertility

After several decades of carefully performed orchiopexies it seems surprising that we still have not answered to everyone's satisfaction the question of whether we really do improve fertility with orchiopexy. Early reports from fertility clinics suggested that orchiopexy can improve fertility in men with unilateral undescended testes but a review of the

literature by Chivers *et al.* (1986) failed to confirm this improvement. What direct evidence is there that the previously undescended testis can subsequently contribute when there is an apparently normal contralateral scrotal testis? The fact that the undescended testis improves histologically is indirect evidence only (Kiesewetter *et al.*, 1969). Even evidence that early operation gives the best fertility results is sparse (Ludwig and Potempa, 1975).

A recent study of a very small number of patients has suggested that a fertility rate of 33% can be achieved by bringing down bilaterally undescended testes (Cendron *et al.*, 1989). Similar results are seen in several reviewed series (Kogan, 1987). Such success in this group of patients is in contrast to the findings of a much quoted report by Ludwig and Potempa (1975) in which all patients with treated bilateral undescend were sterile. Also in the late follow-up series of patients with bilateral impalpable testes subjected to orchiopexy by Puri and O'Donnell (1990) there was uniform azoospermia. These authors also suggested that lesser degrees of undescend are associated with better fertility outcome and that it is the position of the testis rather than whether it is unilateral or bilateral that influences fertility (Puri and O'Donnell, 1988). Is it fair to ask if some, or perhaps many of the fertile men after bilateral orchiopexy had originally had retractile or high scrotal testes? The case is strong for saying that in cryptorchidism both the undescended and the so-called normal contralateral testis are intrinsically abnormal (Hecker and Hienz, 1967). This aspect is well reviewed by Sheldon (1985).

It must be considered whether, despite our good intentions and the time-honoured concept that the main aim of orchiopexy is to increase fertility, we may largely be performing a cosmetic procedure (Colodny, 1986). If this is so then it is still no bad thing to continue performing orchiopexies, since little boys are easily teased for such anomalies, but maybe the time has come to be more honest with ourselves and perhaps the parents of the boys as to our aims and potential achievements.

Classification, statistics and malignancy

In calculating the risks of testicular malignancy in patients with undescended testes, conclusions need to be drawn from reliable statistics or we may continue to give conflicting advice, as we have in the past. The following factors need to be taken into account:

1. There appears to have been an increase in the incidence of undescended testis in the last 2 decades.
2. More orchiopexies appear to be performed now than ever before.
3. 20% of testicular tumours occur in the contralateral testis in patients with unilateral undescend.
4. Testicular tumours are rare but are increasing in incidence.
5. Treatment for testicular cancer is now so successful that the threat to the afflicted patient is not so great as it was.

When we calculated the increased risk of cancer in a patient with undescend in 1970 (Whitaker, 1970) the argument went as follows. The incidence of undescended testis from 1 year onwards was 0.3%, but in large series of testicular tumours 10% of patients had undescended testes; therefore the increased risk was 30 times (10 divided by 0.3). This figure was widely quoted for many years. The equivalent figures now are a 1% incidence of undescended testis after 1 year of age and approximately 7.3% of tumours occurring in patients with undescend. Using these updated figures the increased risk is now reduced to 7.3 times. This considerable reduction may be real or apparent but it does illustrate how a 3-fold increase in the incidence appears to change the risk factor so markedly.

However, for a patient to evaluate his own personal risk over his lifetime, the knowledge of the increased risk is of no value to him by itself. He needs to view this risk in relation to the incidence of testicular tumours in the male population as a whole. Our early calculations for the chances of cancer for an individual adult male with undescend were calculated thus: 2 testis tumours are seen per 100,000 male population (20 per million). Amongst these 20 men per million there will be 2 tumours (10%) in patients with undescend. These 2 must come from the pool of 3000 (0.3%) patients with undescend within that million. Thus there is one patient per 1500 patients with undescend *per annum* afflicted with a testis tumour. (This ignores the fact that 20% of tumours are seen in the contralateral testis). Thus the annual risk of cancer for an adult patient with undescend is 1 in 1500 *per annum* which, in turn, over a risk period of 50 years (20–70 years), gives a 1 in 30 risk.

If the above figures are updated by present day statistics of 4 testis tumours per 100,000 male population, 7.3% of tumours occurring in patients with undescended testis and a 1% incidence of

undescended testis over the age of 1 year, then the lifetime risk appears to be less, at approximately 1 in 70 (Whitaker, 1990). Again one can only question whether this is a real or apparent decrease in the lifetime risk.

When advising an adult man as to whether he should have a unilateral undescended testis removed he may want to know the chances of cure if cancer does occur and its relative risk in comparison to other cancers such as lung, prostate or colon. He may also enquire about the risks of being incapacitated by the anaesthetic or surgery whilst having the testis removed, perhaps in relation to his chances of being knocked down by a car whilst crossing the road. Generally it has been assumed that the risk of dying of testicular cancer is greater than the risk of having the undescended testis removed (Whitaker, 1970; Martin and Menck, 1975). This was probably true for many years but now, with the greatly improved treatment and survival after testicular cancer, it has been suggested that the risks of having an undescended testis removed in adulthood and the risks of succumbing to the cancer become equal at age 32 years (Farrer *et al.*, 1985). Beyond this age the risk of orchiectomy becomes greater than the threat of cancer. This knowledge would be of minimal comfort to most of us.

We probably should be influenced by the position of the testis, as carcinoma *in situ* is far more common in abdominal testes than in ones that are less undescended (Ford *et al.*, 1985). One of the problems is that once the cancer risk is mentioned to the patient, and however logical the argument for conservative management, he will often opt for removal of the testis; we believe that this is a perfectly reasonable decision. In unilateral undescend its removal should not deprive the patient of any hormonal contribution and once the testis has been localised the operation for its removal should be straightforward. In bilateral undescend the theoretical and perhaps occasionally clinical question arises as to whether removal of one testis halves the subsequent risk of malignancy—a question to which we would be loath to address ourselves in our present state of knowledge.

Despite our previous suggestion that early orchiopexy may perhaps lessen the risk of malignancy (Whitaker, 1970), a view also shared by others (Martin, 1981), and despite the view of others based on more adequate statistics that early operation does not help (Pike *et al.*, 1986), there remains a paucity of reports in the literature of patients who have had an early orchiopexy and subsequently

developed malignancy in that testis. It was hoped that orchiopexy might at least make the cancer easier to detect and at an earlier stage; these aspirations have not been achieved (Jones *et al.*, 1991). It is unlikely that we have heard the last word on this issue.

Other Problems

It is extraordinary how few boys with an undescended testis present with clinical evidence of a hernia despite the fact that so many are found to have a patent processus or hernial sac, often of considerable proportions, at orchiopexy. Torsion is probably no more common in an undescended testis than in a normal one, but if the empty scrotum is not examined in a child with abdominal pain the diagnosis may be delayed and the subsequent morbidity increased.

Trauma is often quoted as being more likely to occur in a testis in the groin than in the mobile scrotum but cases of trauma in the undescended testis must be few and far between.

Conclusions

There is a need for a classification on the lines that are suggested here to ensure that all observers abide by the same definitions. The problems that arise from the lack of a classification are illustrated in this review.

Testes probably very rarely descend after the age of 1 year, so that the position of the testis can be established at that time with careful and expert examination. Testes do ascend into a higher position perhaps rather more often than has been reported, but it is our contention that most, if not all of these ascending testes lie just a little higher than normal before ascent occurs. Ascent may also, of course, be seen in a patient who has had a previous herniotomy—the so-called trapped testis.

Orchiopexy can and should give an excellent cosmetic result that allows self-esteem and protection from teasing in the afflicted boy. The contribution that the operation makes to fertility remains uncertain but even if the advantages are small the operation is surely justified to give the patient the benefit of the doubt.

The exact risk of malignancy remains uncertain but the 1992 figures suggest that the increased risk is 7–8 times and that the lifetime risk for an adult with an undescended testis is approximately 1 in 70. These figures can be used as guidelines to advise a patient but in general it is reasonable to remove a

unilateral undescended testis in any fit male who presents over the age of 16 years. In bilateral adult undescended, fortunately now rare, the decision is more difficult, but if the testes are easily observable by ultrasound then an annual scan would at least be one way forward. An alternative would be to remove one testis after bringing one down as far as possible. It remains unclear whether early orchiopexy (under 2 years old), as opposed to an operation at a later age, is beneficial in lessening the cancer risk or improving fertility, but let us hope that another 50 years of discussion will not go by before we can answer this and other questions more accurately.

References

- Atwell, J. D. (1985). Ascent of the testis: fact or fiction *Br. J. Urol.*, **57**, 474–477.
- Beltran-Brown, F. and Villegas-Alvarez, F. (1988). Clinical classification for undescended testes: experience in 1,010 orchidopexies. *J. Pediatr. Surg.*, **23**, 444–447.
- Ceadron, M., Keating, M. A., Huff, D. S. *et al.* (1989). Cryptorchidism, orchiopexy and infertility: a critical long-term retrospective analysis. *J. Urol.*, **142**, 559–562.
- Chivers, C., Dudley, N. E., Gough, M. H. *et al.* (1986). Undescended testis: the effect of treatment on subsequent risk of subfertility and malignancy *J. Pediatr. Surg.*, **21**, 691–696.
- Chivers, C., Pike, M. C., Forman, D. *et al.* (1984). Apparent doubling of frequency of undescended testis in England and Wales in 1962–81. *Lancet*, **ii**, 330–332.
- Colodny, A. H. (1986). Undescended testis—is surgery necessary? *N Engl. J. Med.*, **314**, 510–511.
- Cour-Palais, I. J. (1966). Spontaneous descent of the testicle. *Lancet*, **i**, 1403–1405.
- Farrer, J. H., Walker, A. H. and Rajfer, J. (1985). Management of the postpubertal cryptorchid testis: a statistical review. *J. Urol.*, **134**, 1071–1076.
- Ford, T. F., Parkinson, M. C. and Pryor, J. P. (1985). The undescended testis in adult life. *Br. J. Urol.*, **57**, 181–184.
- Hecker, W. C. and Hienz, H. A. (1967). Cryptorchidism and fertility. *J. Pediatr. Surg.*, **2**, 513–517.
- Jones, B. J., Thornhill, J. A., O'Donnell, B. *et al.* (1991). Influence of prior orchidopexy on stage and prognosis of testicular cancer. *Eur. Urol.*, **19**, 201–203.
- Karpe, B., Eneroth, P. and Ritzén, E. M. (1983). LHRH treatment in unilateral cryptorchidism: effect on testicular descent and hormonal response *J. Pediatr.*, **103**, 892–897.
- Kliesewetter, W. B., Schull, W. R. and Fetterman, G. H. (1969). Histological changes in the testis following anatomically successful orchidopexy. *J. Pediatr. Surg.*, **4**, 59–65.
- Kogan, S. J. (1987). Fertility in cryptorchidism. *Eur. J. Pediatr. (Suppl. 2)*, **146**, S21–S24.
- Ludwig, G. and Potempa, J. (1975). Der optimale Zeitpunkt der Behandlung des Kryptorchismus. *Dtsch. Med. Wochenschr.*, **100**, 680–683.
- Martin, D. C. (1981). Malignancy and the undescended testis. In *The Undescended Testis*, ed. Fonkalsrud, E. W. and Mengel, W. Pp. 144–156. Chicago: Year Book Medical Publishers.
- Martin, D. C. and Menck, H. R. (1975). The undescended testis: management after puberty. *J. Urol.*, **114**, 77–79.

- Moul, J. W. and Belman, A. B. (1988). A review of surgical treatment of undescended testes with emphasis on anatomical position. *J. Urol.*, **140**, 125–128.
- Olsen, L. H. (1989). Inter-observer variation in assessment of undescended testis. *Br. J. Urol.*, **64**, 644–648.
- Pike, M. C., Chivers, C. and Peckham, M. J. (1986). Effect of age at orchidopexy on risk of testicular cancer. *Lancet*, **i**, 1246–1248.
- Puri, P. and O'Donnell, B. (1988). Semen analysis of patients who had orchidopexy at or after seven years of age. *Lancet*, **ii**, 1051–1052.
- Puri, P. and O'Donnell, B. (1990). Semen analysis in patients operated on for impalpable testes. *Br. J. Urol.*, **66**, 646–647.
- Rajfer, J., Handelsman, D. J., Swerdloff, R. S. *et al.* (1986). Hormonal therapy of cryptorchidism. *N. Engl. J. Med.*, **314**, 466–470.
- Schoorl, M. (1982) Classification and diagnosis of undescended testes. *Eur. J. Pediatr.*, **139**, 253–254.
- Sheldon, C. A. (1985). Undescended testis and testicular torsion. *Surg. Clin. North Am.*, **65**, 1303–1329.
- Whitaker, R. H. (1970). Management of the undescended testis. *Br. J. Hosp. Med.*, **4**, 25–37.
- Whitaker, R. H. (1990) The undescended testis. *Postgrad Update*, **41**, 1001–1009.

The Author

R. H. Whitaker, MD, MChir, FRCS, University Lecturer in Paediatric Urology and Honorary Consultant Urologist, Department of Paediatrics.

Requests for reprints to: R. H. Whitaker, 21 High Street, Great Shelford, Cambridge CB2 5EH.

Selective Renal Tumour Biopsy under Ultrasonic Guidance

M. ABE and M. SAITOH

Department of Urology, Kyoto Prefectural University of Medicine, Kyoto, Japan

Summary—Selective renal biopsy under ultrasonic guidance has been used widely because it provides safe and accurate tissue sampling. Using this technique, we biopsied 36 renal tumours and obtained specimens in 35 cases. Histology of the biopsy coincided with that of the surgical specimen in 18/21 cases. Dissemination of tumour cells, thought to have been caused by needle biopsy and/or surgical manipulation, was observed in only 1 case of sarcoma. The method thus proved effective in determining treatment and it is suggested that it should be used in accordance with the criteria which we have devised.

Since the technology for percutaneous renal biopsy by interventional ultrasound was originally developed in 1978 in this clinic, renal biopsy has been performed safely, accurately and easily (Saitoh *et al.*, 1979a and b); because of its precise targeting, we have called the technique “selective renal biopsy” (Saitoh, 1984). At the same time, diagnostic imaging has advanced dramatically, resulting in a remarkable improvement in the detection rate of renal tumours.

Renal biopsy was originally carried out mainly for nephritis and not for renal tumours because of the risk of dissemination of tumour cells and possible bleeding. However, the increasing number of renal tumours detected incidentally by such imaging modalities has changed the situation. If the procedure is followed strictly, a correct diagnosis will be obtained and inappropriate treatment can be avoided.

We have performed biopsy for renal tumours since 1982 according to our own selection criteria (Ohnishi *et al.*, 1983; Watanabe, 1985; Matsuda *et al.*, 1987) and we report our experience.

Patients and Methods

Renal tumour biopsy was performed in 36 patients between June 1982 and May 1990 according to the

“indication standard for selective renal tumour biopsy” by Tomoyoshi and Watanabe (Watanabe, 1985) (Table 1).

The study group comprised 23 males and 13 females aged from 39 to 78 years.

The device used was a mechanical sector scanner with an attachment for needle guidance as used for ordinary selective renal biopsy. A 14G Tru-Cut biopsy needle, a 15G Sure-Cut biopsy needle or an 18G biopsy needle was used, depending on the individual patient.

Results

The results are shown in Table 2.

One of the 36 patients had a 1-cm tumour in the upper pole of the left kidney which could not be detected clearly by ultrasonic imaging, so that

Table 1 Criteria for Selective Renal Tumour Biopsy (Tomoyoshi-Watanabe)

- (1) Not indicated when a radical operation is scheduled.
- (2) Not indicated when it may cause serious complications.
- (3) Indicated when histology provides important information for treatment of patients with inoperable renal tumour.
- (4) Indicated in patients suspected of having a metastatic renal tumour.
- (5) Indicated in patients suspected of having a benign renal tumour by diagnostic imaging.

Table 2 Results

Case no.	Category	Age (years)	Sex	Affected kidney	Size of tumour (cm)	Specimen obtained	Diagnosis by imaging	Histology*	Final diagnosis†	Complications	Significance of biopsy‡
1	3	62	M	Rt	8 × 8	(+)	RCC	TCC	TCC	No	●
2	3	62	M	Lt	9 × 8	(+)	RCC	RCC	RCC	No	○
3	3	73	M	Lt	12 × 10	(+)	RCC	RCC	RCC	No	○
4	3	78	M	Rt	7 × 5	(+)	RCC	TCC	TCC	No	●
5	3	76	M	Rt	5 × 3	(+)	RCC	RCC	RCC	No	○
6	4	63	M	Lt	10 × 10	(+)	RCC	RCC	RCC	No	○
7	4	70	M	Lt	8 × 7	(+)	RCC	Medullary fibroma	AML	Dissemination	×
8	4	71	M	Lt	10 × 8	(+)	RCC	RCC	RCC	No	○
9	4	79	M	Rt	10 × 10	(+)	RCC	RCC	RCC	No	○
10	4	73	M	Rt	9 × 5	(+)	RCC	Metastatic SCC	SCC	No	○
11	4	71	M	Lt	5 × 4	(+)	RCC	SCC	SCC	No	●
12	4	77	M	Lt	6 × 5	(+)	RCC	Atypia	Metastatic renal carcinoma	No	×
13	5	68	F	Lt	6 × 5	(+)	Not specified	RCC	RCC	No	○
14	5	67	M	Rt	5 × 5	(+)	Not specified	RCC	RCC	No	○
15	5	41	F	Lt	2 × 2	(+)	Not specified	Normal	Bertin's column	No	●
16	5	51	F	Lt	2 × 2	(+)	Not specified	RCC	RCC	No	○
17	5	54	M	Lt	3 × 3	(+)	AML	AML	AML	No	○
18	5	77	M	Rt	5 × 4	(+)	Not specified	RCC	RCC	No	○
19	5	78	M	Lt	8 × 7	(+)	Not specified	RCC	RCC	No	○
20	5	38	M	Lt	4 × 4	(+)	Not specified	RCC	RCC	No	○
21	5	76	M	Lt	4 × 4	(+)	Sinus lipomatosis	Sinus lipomatosis	Sinus lipomatosis	No	●
22	5	73	M	Rt	4 × 4	(+)	Not specified	TCC	TCC	No	●
23	5	53	F	Lt	10 × 5	(+)	Not specified	XP	XP	No	●
24	5	62	M	Rt	2 × 2	(+)	AML	RCC	RCC	No	●
25	5	72	F	Rt	2 × 1	(+)	Not specified	TCC	TCC	No	●
26	5	65	F	Lt	5 × 5	(+)	Not specified	XP	XP	No	●
27	5	41	F	Rt	3 × 2	(+)	Not specified	Normal	Bertin's column	No	●
28	5	52	F	Rt	2 × 2	(+)	AML	AML	AML	No	○
29	5	53	M	Lt	4 × 3	(+)	Not specified	Normal	Bertin's column	No	○
30	5	39	F	Rt	4 × 4	(+)	Not specified	RCC	RCC	No	○
31	5	47	F	Lt	10 × 4	(+)	Not specified	TCC	TCC	No	○
32	5	55	F	Rt	3 × 3	(+)	Not specified	RCC	RCC	No	○
33	5	69	F	Lt	1 × 1	(-)	Not specified	—	RCC	—	×
34	5	40	M	Lt	4 × 4	(+)	Not specified	RCC	RCC	No	○
35	5	74	F	Rt	3 × 2	(+)	Infarction	Necrosis	Infarction	No	○
36	5	40	M	Rt	10 × 9	(+)	Not specified	Angioma	Angioma	No	●

* RCC: Renal carcinoma. TCC: Transitional cell carcinoma. SCC: Squamous cell carcinoma. AML: Angiomyolipoma. XP: Xanthogranulomatous pyelonephritis.

† The diagnoses in italics were confirmed by surgery, others only by biopsy.

‡ ●: Very significant, ○: Significant, ×: Not significant.

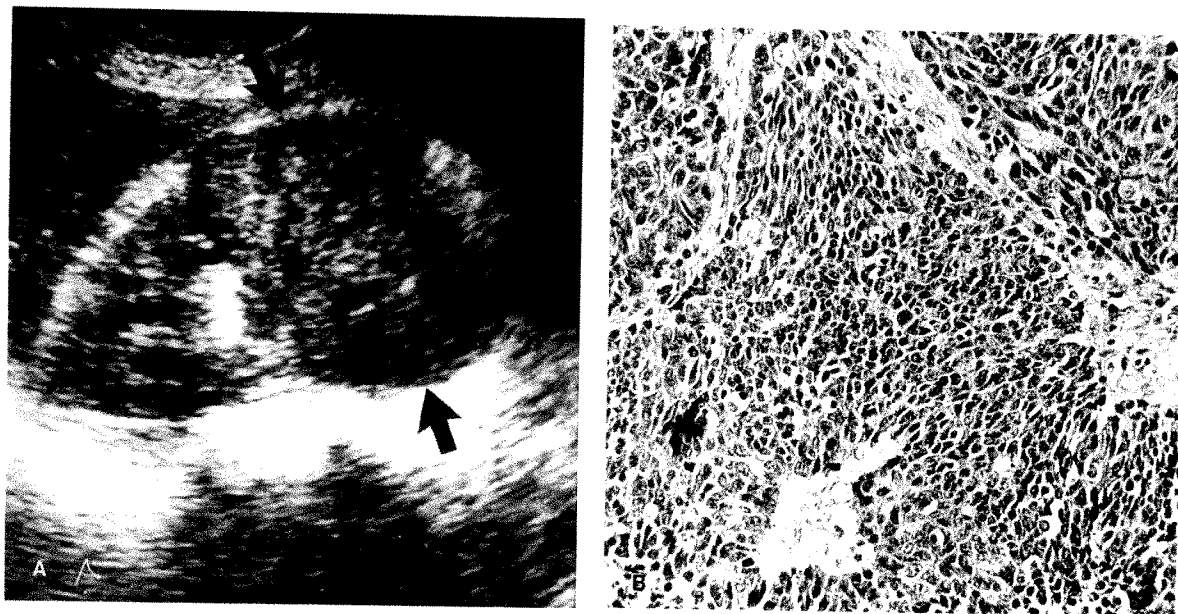


Fig. 1 (A) Case 4. Ultrasound demonstrated a solid renal mass thought to be renal carcinoma (arrow). (B) Histological diagnosis by biopsy revealed transitional cell carcinoma. ($\times 400$)

biopsy was unsuccessful. In the remaining 35 cases, specimens from the tumour were obtained successfully.

The tumours ranged in size from 1×1 to 12×10 cm and 36 tumour biopsies were classified according to our criteria (Table 1); 5 were category 3, 7 were category 4 and 24 were category 5.

In category 3, 3 patients were finally diagnosed as having renal carcinoma and 2 had transitional cell carcinoma (Fig. 1). In category 4, 3 patients had metastatic renal tumours and 4 had renal carcinoma with other tumours at other sites. In category 5, 10 patients had benign tumours and 14 had malignant lesions. The final diagnosis in the 10 cases of benign tumour was Bertin's column (3 cases), angiomyolipoma (2) (Fig. 2), xanthogranulomatous pyelonephritis (2), sinus lipomatosis (1), renal infarction (1) and haemangioma (1).

The final diagnosis in the 14 patients with malignant tumours was renal carcinoma (11) (Fig. 3) and transitional cell carcinoma (3).

Of the 36 biopsies, diagnosis was confirmed by surgery in 21. Histology of the biopsy coincided with that of the surgical specimen in 18 cases (86%). In 1 of the 3 cases (No. 33) in which the correct diagnosis could not be made from the biopsy, tumour tissue was not included in the specimen because the tumour was too small. In another histologically mismatched case (No. 7) the biopsy

disclosed medullary fibroma but histology of the extirpated specimen revealed angiomyolipoma. Two years and 6 months after the initial operation, local tumour recurrence was noted (probably seeded by the puncture and/or surgical manipulation). Histology of the recurrent tumour was liposarcoma. In this case the diagnosis of angiomyoliposarcoma should have been made in the first instance. In the remaining case (No. 12), histology by biopsy demonstrated atypia but could not be specified. Histological evaluation of the extirpated specimen was also very difficult. In this case a metastatic renal tumour was suspected but the primary lesion could not be determined.

No complications were observed in this series. No tumour seeding has been found during follow-up ranging from 1 to 7 years, except for the one case of angiomyoliposarcoma (No. 7) described above.

Discussion

Dramatic advances in imaging techniques, such as ultrasound and CT, have revealed many incidental, asymptomatic renal tumours. Whether these tumours are benign or malignant cannot be defined by ultrasound or CT and even angiography may not lead to a correct diagnosis. Laparotomy is invariably required in such cases. Adequate treat-

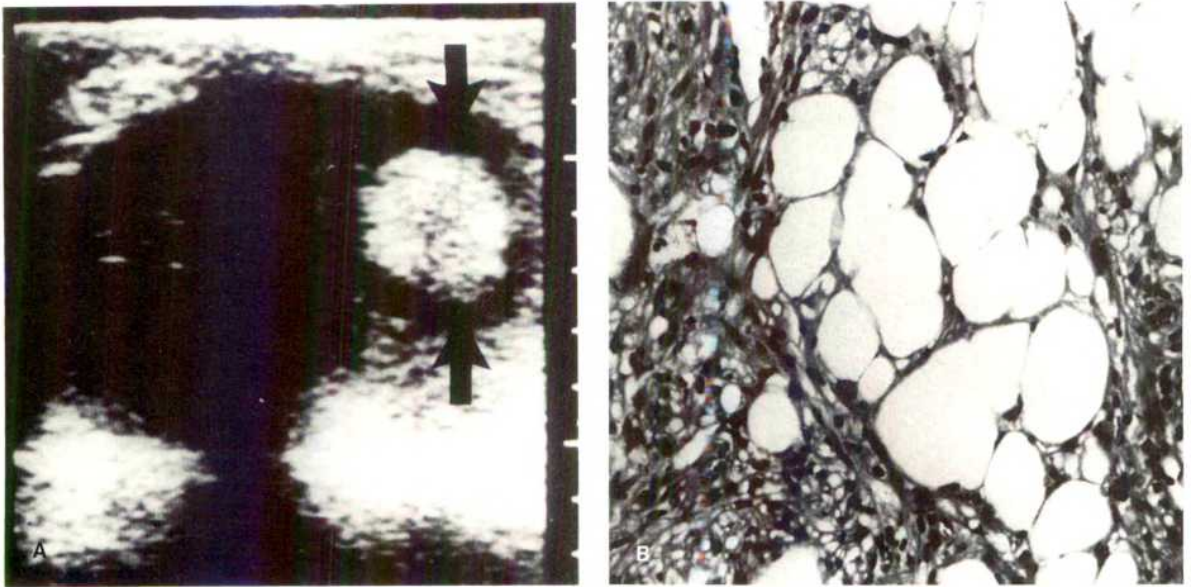


Fig. 2 (A) Case 17. A hyperechoic mass was detected by ultrasound (arrows). (B) Histological diagnosis by biopsy revealed angiomyolipoma. ($\times 400$)

ment cannot be determined unless the diagnosis is correct and every effort should be made to achieve this.

Histological examination by biopsy has not been used for the kidneys because of the risk of bleeding and the seeding of tumour cells. In addition, there has been no satisfactory technique for the selective

puncturing of renal tumours. The development of interventional ultrasound has made it possible for percutaneous renal biopsy to be carried out safely and accurately and the risk of bleeding is now similar to that associated with biopsy of other organs. In addition, the risk of seeding tumour cells is not appreciably greater for the kidneys than for

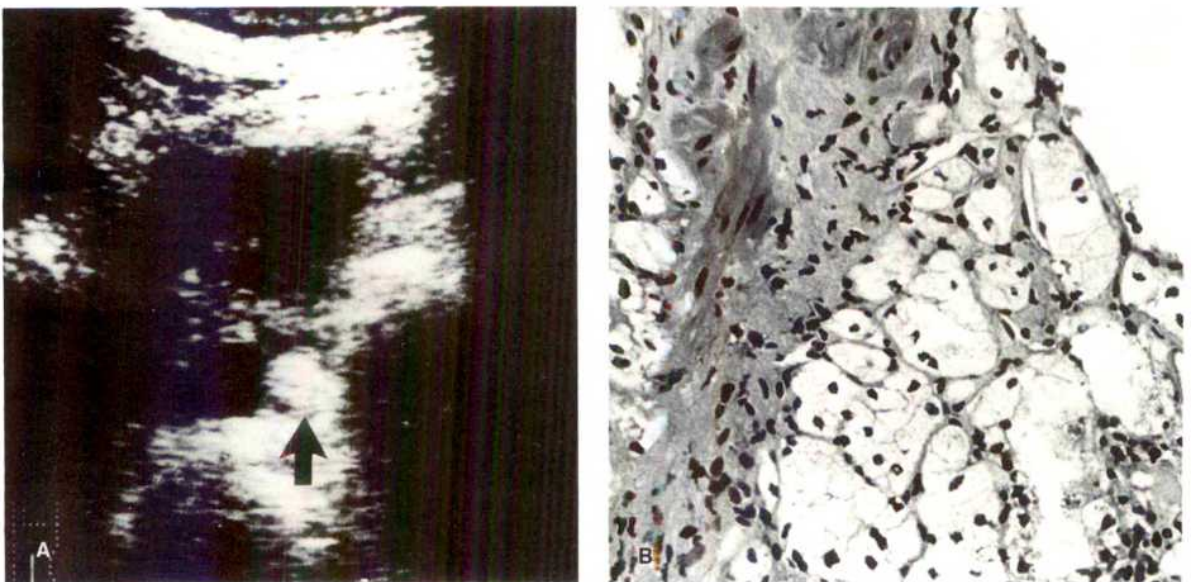


Fig. 3 (A) Case 24. A small hyperechoic mass was revealed by ultrasound (arrow). (B) Histological diagnosis by biopsy revealed renal carcinoma. ($\times 400$)

other organs (Auvert *et al.*, 1982; Juul *et al.*, 1985; George and Kaufman, 1966). We found seeding in only 1 case of angiosarcoma 2.5 years after biopsy, when the possibility of seeding due to surgical manipulation was also recognised. No tumour spread after biopsy was encountered in cases of either renal or transitional cell carcinoma. According to Smith (1985), the probability of seeding by fine needle aspiration is very low, *i.e.* 3/63,108 cases (0.005%). Kaufman and Schultz (1962) reported that seeding as a result of biopsy of prostatic tumours from the cutting needle was observed in only 1 of 658 cases (0.15%). Although there have been no reports on the seeding of renal carcinoma by needle biopsy based upon a large number of cases, the probability of seeding seems to be less than generally supposed. The cost-benefit balance between the advantages of biopsy and the disadvantages of complications should be considered. For that reason, the criteria for renal tumour biopsy (Table 1) have been strictly observed.

We experienced only 1 failure to collect the specimen (No. 33). The histological diagnosis by biopsy and the diagnosis of the excised specimen did not coincide in 1 case of angiosarcoma (No. 7) and in another case of metastatic tumour (No. 12) which was not specified because of too few atypical cells in the specimen. In these 3 patients (8%), renal tumour biopsy was inadequate (Table 2). Apart from these, neither false positive nor false negative cases were found in this series.

Of 33 cases (92%) in which the correct diagnosis was obtained by biopsy, the method revealed a special significance in 16 (44%) (Table 2).

The diagnosis on biopsy was transitional or squamous cell carcinoma in 7 cases but the diagnosis by imaging modalities prior to biopsy was renal carcinoma in 4 cases (Nos 1, 4, 10, 11) and undetermined as to whether the tumour was benign or malignant in 3 cases (Nos 22, 25, 31). Biopsy confirmed benign tumours in 8 cases (Nos 15, 21, 23, 26, 27, 29, 35, 36) but imaging modalities were unable to confirm this in all of them. On the other hand, a typical hyperechoic mass was revealed by ultrasound in Case 24 (Fig. 3). This is believed to be a sign of angiosarcoma, and biopsy revealed renal carcinoma.

Comparison of fine needle aspiration biopsy with cutting needle biopsy shows that the former may be safer with regard to seeding, but the latter is better in terms of accurate tissue sampling. As shown in

our criteria, a false negative result (which might occur more often with aspiration than with needle biopsy) cannot be overlooked. A Tru-Cut needle was used routinely in this series and resulted in tissue sampling without complications.

The Tomoyoshi-Watanabe criteria (Table 1) present no problems at present, but certain points may need revision (*e.g.* category 1) as the scope of imaging and treatment techniques becomes wider.

Acknowledgement

We thank Professor H. Watanabe for his helpful advice and for reviewing the manuscript.

References

- Auvert, J., Abbon, C. C. and Lavarenne, V. (1982). Needle tract seeding following puncture of renal oncocytoma. *Prog. Clin. Biol. Res.*, **100**, 597-598.
- George, V. and Kaufman, J. J. (1966). Local implantation of carcinoma of the prostate with percutaneous needle biopsy. *J. Urol.*, **95**, 801-804.
- Juul, N., Pederson, S. and Larsen, S. (1985). Puncture of renal mass lesions. In *Interventional Ultrasound*, ed. Holm, H. H and Kristensen, J. K. Pp. 84-90. Munksgaard: Copenhagen.
- Kaufman, J. J. and Schultz, J. I. (1962). Needle biopsy of the prostate: a re-evaluation. *J. Urol.*, **87**, 164-168.
- Matsuda, T., Saitoh, M., Abe, M. *et al.* (1987). Selective renal biopsy for renal tumor. *Jpn. J. Urol.*, **78**, 1417-1422.
- Ohnishi, K., Watanabe, H., Saitoh, M. *et al.* (1983). A case of renal transitional cell carcinoma diagnosed by selective renal biopsy using ultrasonically guided puncture. *Jpn. J. Med. Ultrasonics*, **10**, 419-422.
- Saitoh, M. (1984). Selective renal biopsy under ultrasonic real-time guidance. *Urol. Radiol.*, **6**, 30-37.
- Saitoh, M., Watanabe, H., Obe, H. *et al.* (1979a). Ultrasonically guided puncture technique in urology using real-time scanner. *Jpn. J. Urol.*, **70**, 46-52.
- Saitoh, M., Watanabe, H., Obe, H. *et al.* (1979b). Ultrasonic real-time guidance for percutaneous puncture. *J. Clin. Ultrasound*, **7**, 269-272.
- Smith, E. H. (1985). Fine-needle aspiration biopsy: are there any risks? In *Interventional Ultrasound*, ed. Holm, H. H. and Kristensen, J. K. Pp. 169-177. Munksgaard: Copenhagen.
- Watanabe, H. (1985). Interventional ultrasound in urology. The 34th Central Section Meeting of the Japanese Urological Association: Symposium II. *Acta. Urol. Jpn.*, **31**, 1257-1258.

The Authors

M. Abe, MD, Assistant.

M. Saitoh, MD, Assistant Professor.

Requests for reprints to: M. Saitoh, Department of Urology, Kyoto Prefectural University of Medicine, Kawaramachi-Hirokoji, Kyoto, Japan.

Effect of Vaginal Ultrasound Probe on Lower Urinary Tract Function

B. G. WISE, G. BURTON, A. CUTNER and LINDA D. CARDOZO

Urodynamic Unit, King's College Hospital, London

Summary—Vaginal ultrasonography has been advocated as an alternative to videocystourethrography. Ultrasound avoids the potential risks of X-rays and reduces the cost of equipment. We have investigated the effect of the vaginal probe on the physiology of the bladder and urethra. A series of 24 women underwent urethral pressure profilometry, with and without a vaginal probe *in situ*. There was a significant increase in maximum urethral pressure, functional urethral length and area under the profile curve both at rest and during stress in the presence of the device. This was due to stretching and compression of the urethra by the probe. Transmission pressure ratios were significantly increased for the first 3 quartiles of the urethra.

Twenty women underwent lateral bead chain urethrocystography with and without a vaginal probe. At rest, the probe resulted in elevation of the bladder neck and apposition to the symphysis pubis, and during a Valsalva manoeuvre the descent of the bladder neck was restricted by the presence of the probe. These results indicate that a vaginal probe alters the position and function of the lower urinary tract. We postulate that incontinence is reduced as a result of the probe. The use of vaginal ultrasonography in the assessment of women with urinary incontinence is therefore not recommended.

X-ray imaging remains the commonest method employed to visualise the lower urinary tract. Its use is combined with subtracted provocative cystometry, so that videocystourethrography is still regarded as the “gold standard” in the assessment of the incontinent patient (Turner-Warwick, 1979). Recently, however, ultrasonography has been advocated as an alternative imaging technique for the lower urinary tract. The use of ultrasound to visualise abdominopelvic structures dates back to the 1950s (Donald *et al.*, 1958), but assessment of the bladder was limited to estimation of urinary volume, bladder wall mobility and distortion by pelvic masses, and the detection and evaluation of bladder tumours (Holmes, 1971).

The degree of descent of the urethrovesical junction during stress episodes was assessed by White *et al.* (1980), using a linear array abdominal scanner. A similar technique was employed to

determine bladder neck mobility before and after retropubic urethropexy (Bhatia *et al.*, 1987). The problem of “shadowing” of the urethrovesical junction by the symphysis pubis was reported by both authors and limits the application of this technique.

Transrectal ultrasonography has been used as an alternative to lateral chain cystography in the assessment of anatomical support of the urethrovesical junction (Bergman *et al.*, 1988). It has been shown that the presence of the rectal probe has no significant effect on the urodynamic parameters measured in patients undergoing cystometry, urethral pressure profilometry and a fluid bridge test (Richmond and Sutherst, 1989).

Vaginal ultrasonography has been proposed as a suitable alternative to videocystourethrography in the assessment of urinary incontinence (Quinn *et al.*, 1988; Koelbl and Bernaschek, 1989). This method is attractive in that it is simple to perform, the equipment required is found in many gynaecological units, and the risks of irradiation to patient

and operator are removed. Quinn *et al.* (1988) suggested that any distortion of urethrovesical anatomy caused by the probe may be detected and thus avoided, but no objective evidence of this was given. Modern vaginal probes are thin and give good visualisation of the lower urinary tract when placed only a short distance into the vagina (Koebl and Bernaschek, 1989), but it is not known how the probe itself affects the function of the lower urinary tract.

This study was undertaken to evaluate the effects, if any, of a vaginal ultrasound probe on the urodynamics of the lower urinary tract.

Patients and Methods

A total of 44 women who attended this urodynamic unit, complaining of urinary incontinence, were included in the study. Each patient gave a full history and underwent routine urodynamic investigation, comprising uroflowmetry, subtracted provocative cystometry and videocystourethrography. Any woman with gross uterovaginal prolapse was excluded.

In 24 cases a urethral pressure profile was performed (by B.G.W.) with and without a vaginal ultrasound probe *in situ*. The technique was as described by Hilton and Stanton (1983), using a Gaeltec catheter with 2 solid state, microtip transducers mounted 6 cm apart. Recordings were taken with the subject supine, with 250 ml of physiological saline in the bladder. The orientation of the transducers was lateral (9 o'clock). Resting and stress profiles were obtained with and without the probe present. The probe was positioned by an expert vaginal ultrasonographer (G.B.) approximately 2 cm inside the vaginal introitus in a functional position to enable the bladder and urethrovesical junction to be constantly visualised without obviously distorting the anatomy of the area. In this study we used the vaginal probe from a Siemens S.L.2 ultrasound machine. This probe is a maximum of 1.7 cm wide and has the advantage of both variable frequency settings and a variable direction internal probe. All images were taken using 6.5 MHz frequency. Functional urethral length (FUL), maximum urethral pressure (MUP) and transmission pressure ratios (TPRs), calculated for each quartile of urethral length, were recorded on each occasion.

Twenty women underwent lateral bead chain cystography to assess the position of the bladder neck at rest and its descent on coughing and during a Valsalva manoeuvre. The same ultrasound probe

was then inserted into the vagina, in a functional position, and the investigation was repeated. Lignocaine gel 1% was used to anaesthetise the urethra and facilitate insertion of the bead chain. The resting position of the bladder neck and its excursion on straining and coughing were recorded on videotape. Figure 1 shows the measurements that were taken. The distance "b" from the urethrovesical junction to the lower border of the symphysis pubis was measured at rest. The angles "a", "c" and "d" were also calculated. Angle "c" represents the posterior urethrovesical angle and "d" is the urethral curve. All 4 parameters were obtained at rest and at maximum Valsalva manoeuvre. Values obtained in the absence of the probe were compared with those measured with the probe *in situ*. The measurements were made by an independent observer (A.C.).

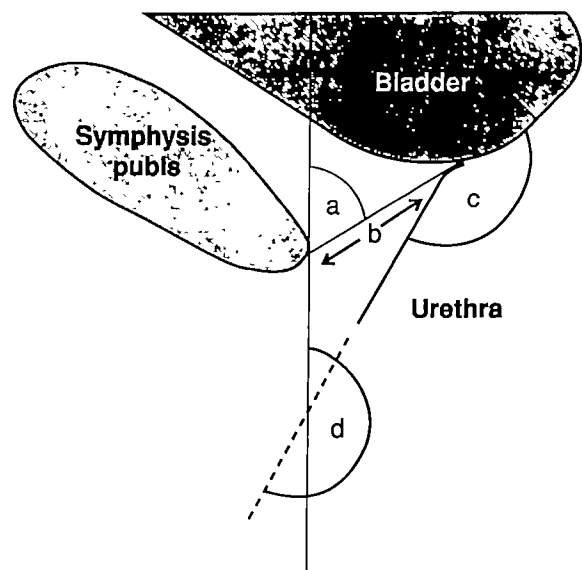


Fig. 1 Diagram of bladder neck and urethra, showing the angles and distances measured.

Results

Urethral pressure profilometry

The resting values of maximum urethral pressure, functional urethral length and area under the profile were significantly greater when the vaginal probe was present (Table 1). This was also true for the stress profile (Table 2). Table 3 shows the transmission pressure ratios (TPR), expressed as a percentage, for each quartile of urethral length. There is a

Table 1 Statistical Analysis of Resting UPP Parameters with and without the Vaginal Probe. (Wilcoxon matched pairs test) (n = 24)

Value	Out (mean)	In (mean)	P
MUP (cm H ₂ O)	52.7	83.0	<0.0001
FUL (mm)	30.1	40.5	=0.0002
Total area (mm ²)	654	1178	<0.0001

MUP = Maximum urethral pressure.

FUL = Functional urethral length.

Total area = Area under urethral pressure profile.

Table 2 Statistical Analysis of Stress UPP Parameters with and without the Vaginal Probe. (Wilcoxon matched pairs test) (n = 23)

Value	Out (mean)	In (mean)	P
MUP (cm H ₂ O)	33.7	58.0	=0.0002
FUL (mm)	25.4	31.4	=0.0006
Total area (mm ²)	360	832	=0.0003

Table 3 Statistical Analysis of Transmission Pressure Ratios for each Quartile of Urethral Length, with and without the Probe. (Wilcoxon matched pairs test) (n = 21)

Quartile	Out (mean) (%)	In (mean) (%)	P
M 25	91.0	99.1	0.021
M 50	91.1	102.8	0.025
M 75	86.2	105.0	0.019
M 100	46.3	62.6	0.170

significant increase in TPR with the probe *in situ* for the proximal 3 quartiles. In the presence of the probe, supraphysiological TPR values (*i.e.* >100%) were obtained in the second and third quartiles. Usually such high values are only found following intervention such as incontinence surgery.

Lateral bead chain urethrocystography

The results are shown in Table 4 and graphically in Figure 2. There was a significant reduction in angle "a" both at rest and during stress in the presence of the ultrasound probe ($P < 0.001$). No change in the distance "b" from the bladder neck to the lower border of the symphysis was observed either at rest or maximal strain. The posterior urethrovesical

angle "c" was significantly reduced, both at rest and on Valsalva, with the probe *in situ* ($P < 0.05$). Similarly, there was a significant reduction in angle "d" at rest ($P < 0.05$) and during stress ($P < 0.005$) with the probe in the vagina (Table 5).

Discussion

This is the first report of the physical effect of the vaginal probe while visualising the lower urinary tract with vaginal ultrasonography. The increase in resting MUP and FUL suggests that the vaginal probe causes compression and stretching of the urethra. The improvement in pressure transmission to the proximal three-quarters of the urethra is

Table 4 Results of Lateral Bead Chain Urethrocystography with and without the Probe. (See Fig. 1)

		Median	IQR	Range
Rest probe out	a	70	56.5–80	10–100
	b	32.5	28–41	22–47
	c	127.5	110–140	60–160
	d	198	171–212.5	135–255
Rest probe in	a	47.5	32.5–70.5	0–110
	b	34.5	30–40	24–49
	c	107.5	90–131	52–155
	d	185.5	165–200	133–250
Strain probe out	a	94	77.5–101	20–112
	b	35	30–38	24–54
	c	130	116.5–152.5	57–175
	d	222.5	202.5–247.5	120–255
Strain probe in	a	67.5	59–87.5	0–120
	b	34.5	30–37	24–49
	c	117.5	91–135	40–150
	d	196	170–215	117–250

(IQR = Interquartile range).

Table 5 Statistical Analysis of Lateral Bead Chain Urethrocystography Parameters, with and without the probe. (Wilcoxon matched pairs test) (n = 20)

	Value	Probe out (median)	Probe in (median)	P
Rest	a	70	47.5	0.0008
	b	32.5	34.5	0.7226
	c	127.5	107.5	0.0386
	d	198	185.5	0.460
Strain	a	94	67.5	0.0006
	b	35	34.5	0.4200
	c	130	117.5	0.260
	d	222.5	196	0.0016

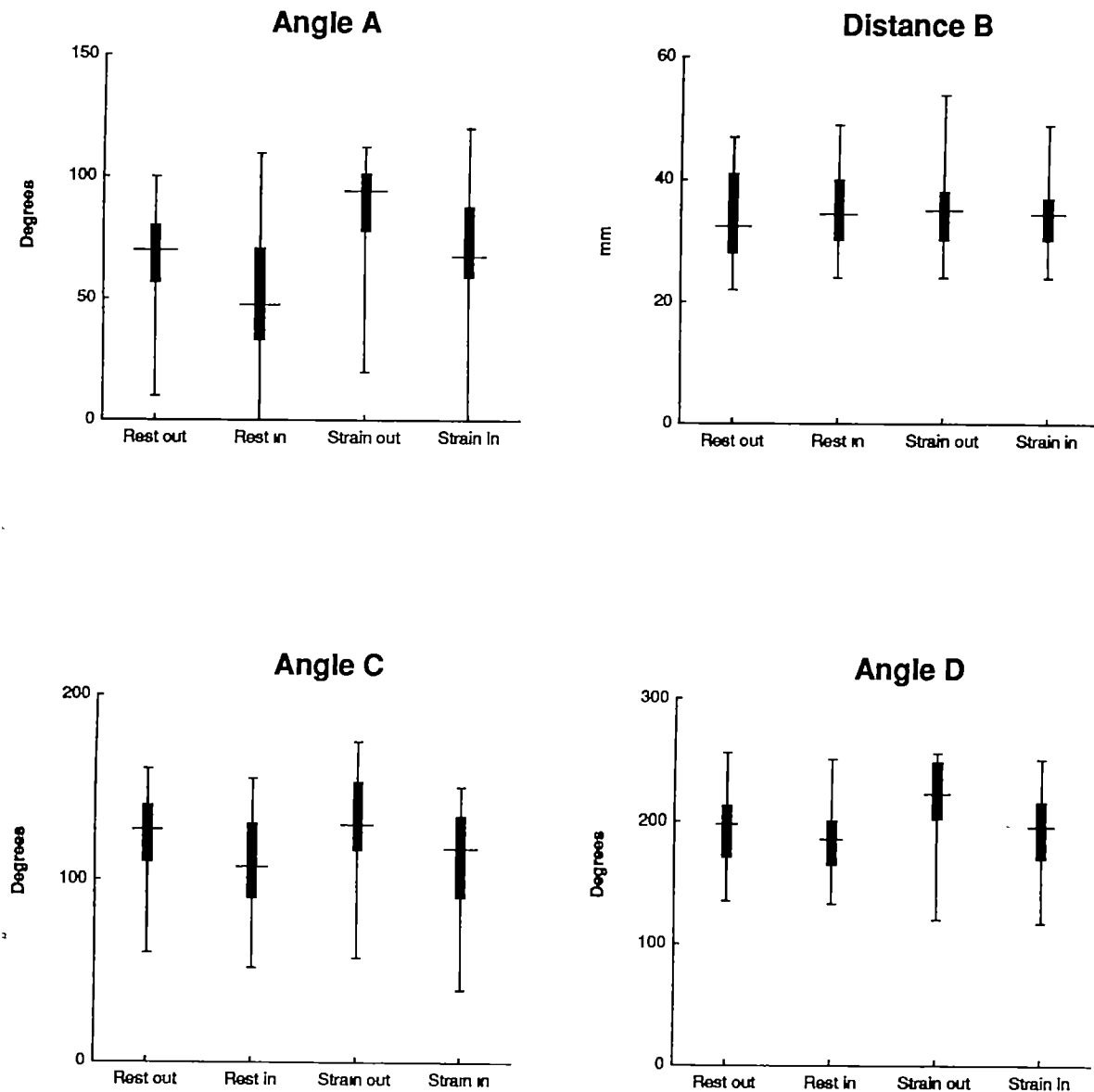


Fig. 2 Diagram to show the effect of a vaginal ultrasound probe on lateral bead chain cystourethrography parameters. (Median, interquartile range and range).

possibly due to elevation of the bladder neck by the probe, despite the fact that the probe was inserted only just into the introitus and any obvious distortion of the anatomy was avoided. The results of lateral chain urethrocytography confirm that this is in fact the case (Fig. 3). The position of the bladder neck at rest is elevated and apposed to the symphysis pubis in the presence of the probe. This movement is similar to that obtained during pelvic floor contraction. During a Valsalva manoeuvre, descent of the bladder neck is restricted by the

presence of the ultrasound probe. This combination of elevation of the bladder neck and compression of the urethra has profound implications for the use of vaginal ultrasonography in the assessment of women with urinary incontinence and in particular those with genuine stress incontinence.

Genuine stress incontinence (GSI) is defined as the involuntary loss of urine that occurs when the intravesical pressure exceeds the maximum urethral pressure in the absence of detrusor activity. Transmission of intra-abdominal pressure to the proximal

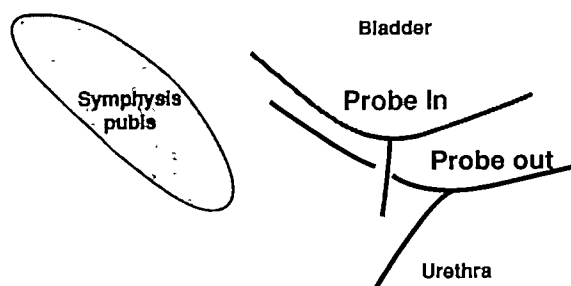


Fig. 3 Bladder neck position at rest, with and without the vaginal probe.

urethra during stress episodes is an important factor in the maintenance of continence. This is achieved if the bladder neck and proximal urethra are situated intra-abdominally above the pelvic floor. Descent of the bladder neck below the pelvic floor results in loss of pressure transmission such that intravesical pressure may exceed maximum urethral pressure during stress, and incontinence occurs. Surgical treatment of GSI attempts to elevate and fix the bladder neck retropubically and thus improve pressure transmission to the urethra.

The use of a vaginal probe results in compression of the urethra, increased urethral pressure, elevation of the bladder neck and improved pressure transmission to the proximal urethra. It may therefore reduce the likelihood of detecting incontinence in women with GSI or reduce the severity of GSI diagnosed. Detrusor instability is a functional abnormality of the detrusor muscle which causes rises in detrusor muscle pressure; ultrasound is unable to visualise the pressure changes associated with that condition but even leakage associated with detrusor instability may be reduced as a result of increased urethral pressure caused by the probe.

For these reasons, therefore, vaginal ultrasonography cannot be recommended for the assessment of morphological abnormalities. In addition, it may

be inappropriate to assess the descent and mobility of the bladder neck, and prolapse, by means of vaginal ultrasonography.

References

- Bergman, A., McKenzie, C. J., Richmond, J. *et al.* (1988). Transrectal ultrasound versus cystography in the evaluation of anatomical stress urinary incontinence. *Br. J. Urol.*, **62**, 228–234.
- Bhatia, N. N., Ostergard, D. R., McQuown, D. *et al.* (1987). Ultrasonography in urinary incontinence. *Urology*, **29**, 90–94.
- Donald, I., Macvicar, J. and Brown, T. (1958). Examination of abdominal masses by pulsed ultrasound. *Lancet*, **1**, 1118.
- Hilton, P. and Stanton, S. L. (1983). Urethral pressure measurement by microtransducer: the results in symptom free women and in those with genuine stress incontinence. *Br. J. Obstet. Gynaecol.*, **90**, 919–933.
- Holmes, J. H. (1971). Ultrasonic studies of bladder filling and contour. In *Hydrodynamics of Micturition*, ed. Hinman, F. J. P. 303. Springfield: Thomas
- Kochl, H. and Bernaschek, G. (1989). A new method for sonographic urethrocytography and simultaneous pressure-flow measurements. *Obstet. Gynaecol.*, **74**, 417–422.
- Quinn, M. J., Beynon, J., Mortenson, N. J. McC. *et al.* (1988). Transvaginal endosonography: a new method to study the anatomy of the lower urinary tract in urinary stress incontinence. *Br. J. Urol.*, **62**, 414–418.
- Richmond, D. H. and Sutherst, J. (1989). Transrectal ultrasound scanning in urinary incontinence: the effect of the probe on urodynamic parameters. *Br. J. Urol.*, **64**, 582–585.
- Turner-Warwick, R. (1979). The evaluation of urodynamic function. *Urol. Clin. North Am.*, **6**, 51–54.
- White, R. D., McQuown, D., McCarthy, T. A. *et al.* (1980). Real-time ultrasonography in the evaluation of urinary stress incontinence. *Am. J. Obstet. Gynaecol.*, **138**, 235–237.

The Authors

B. G. Wise, MB, BS, Research Fellow.
 G. Burton, FRACOG, Research Fellow
 Linda D. Cardozo, MD, FRCOG, Consultant Obstetrician and Gynaecologist.
 A. Cutner, MB, BS, Research Fellow.

Requests for reprints to: B. G. Wise, Department of Urodynamics, King's College Hospital, Denmark Hill, London SE5 9RS.

Detrusor Mast Cells in Refractory Idiopathic Instability

KATE H. MOORE, P. NICKSON, D. H. RICHMOND, J. R. SUTHERST, P. R. MANASSE and T. R. HELLIWELL

Departments of Obstetrics and Gynaecology and Department of Pathology, University of Liverpool, Liverpool

Summary—The diagnosis of interstitial cystitis (IC) is not usually considered in patients with idiopathic instability. Because histamine provokes detrusor contractions *in vitro*, we assessed detrusor mast cell counts in 29 females with refractory instability. Raised mast cell counts ($> 28/\text{mm}^2$ of detrusor muscle, consistent with a histological diagnosis of IC) were found in 29% of such cases. Thus cystoscopy and bladder biopsy should be considered in patients with idiopathic instability which fails to respond to anticholinergic drugs, as alternative therapy may be useful.

Patients with refractory instability and normal detrusor mast cell counts often gave a history of prolonged childhood nocturnal enuresis (55% of cases); in contrast, patients with intractable instability and abnormally high mast cell counts seldom gave such a history (12%). These trends may give some insight into the aetiology of idiopathic instability—"congenital" or acquired?

Patients with the clinical and urodynamic features of idiopathic detrusor instability are not usually regarded as candidates for the diagnosis of interstitial cystitis (George, 1986). The majority of patients with interstitial cystitis (IC) have stable, small capacity bladders, though the cystometric finding of systolic detrusor waves does not exclude the diagnosis (Hald and Holm-Bentzen, 1986; Perez-Marrero *et al.*, 1987). Indeed the latter authors found detrusor instability in 13 of 50 IC patients.

Controversy remains as to whether "detrusor mastocytosis" is essential to the diagnosis of interstitial cystitis. Larsen *et al.* (1982) found detrusor mast cell counts $> 62 \pm 8/\text{mm}^2$ in all patients with frank clinical and cystoscopic features of the disease. Patients with the clinical features alone (chronic suprapubic pain and severe frequency of micturition) had 28 ± 8 mast cells/ mm^2 of detrusor muscle. Kastrup *et al.* (1983) and Feltis *et al.* (1987) also found that a mast cell count $> 20/\text{mm}^2$ was a useful marker for the diagnosis of IC.

For patients with idiopathic detrusor instability, the cystometric findings are commonly regarded as sufficient abnormality to account for their

symptoms; cystoscopy is not routinely recommended (Messing, 1987). Several authors suggest that the condition is psychosomatic in origin (Hafner *et al.*, 1977; Frewen, 1978; Macauley *et al.*, 1987). However, recent studies have cast doubt upon the aetiological role of psychological disturbance in idiopathic instability (Morrison *et al.*, 1986; Moore and Sutherst, 1990; Norton *et al.*, 1990).

In vitro studies have shown that histamine, which is released from mast cells, may provoke contractions in organ bath preparations of mammalian (Ambache and Zar, 1970; Rubenstein *et al.*, 1985) and human (Todd and Mack, 1969; Rubenstein *et al.*, 1986) detrusor muscle. Such histamine-evoked detrusor contractions were found to be atropine-resistant.

Therefore we undertook a study of the distribution of mast cells in the detrusor muscle of patients with idiopathic detrusor instability who had failed to respond to anticholinergic drugs.

Patients and Methods

Refractory detrusor instability (DI) was defined as follows. (1) Idiopathic detrusor instability of > 15 cm pressure rise during medium fill cystometry

without evidence of voiding difficulty on free uroflowmetry. (2) Duration of symptoms > 4 years. (3) Failure to respond to at least 2 anticholinergic drugs coupled with out-patient bladder training for more than 1 year. (4) Persistent disabling symptoms of frequency/urgency/incontinence documented on a frequency volume chart.

All such patients seen during an 18-month recruitment period at a gynaecological urodynamic follow-up clinic were admitted for in-patient bladder training (performed by K.H.M.). If this final attempt at conservative treatment was unsuccessful, cystoscopy and refill examination to detect petechial haemorrhages was performed. Of the 39 patients admitted on this basis, 8 responded to in-patient bladder drill and 2 declined to remain in hospital for cystoscopic examination; 29 females (median age 47 years, range 21–70) underwent endoscopic bladder biopsy.

Clinical factors such as the number of voids/24 h at the time of admission, a history of nocturnal enuresis beyond the age of 6 years, maximum detrusor pressure during filling cystometry performed at initial diagnosis, and cystoscopic bladder capacity at the time of biopsy were recorded prospectively in order to detect any clinical trends in patients with normal or raised mast cell counts.

Control biopsies were taken from 17 women (median age 53 years, range 29–73) with haematuria but no frequency or urgency of micturition or acute bacterial cystitis. In view of the 33% incidence of detrusor instability known to occur after previous pelvic irradiation for gynaecological cancer (Parkin *et al.*, 1988), such patients were also excluded.

Cold-cup bladder biopsies were taken from the lateral wall of the bladder; specimens were fixed in parabenzoquinin (to allow immunohistochemical examination as part of a separate study of vasoactive intestinal polypeptide (Moore *et al.*, 1991)). Cryostat sections were stained with 4% pararosanilin/AS-D chloroacetate according to the method of Leder (1970) in order to produce optimal mast cell staining (Frazer, 1988).

The effect of parabenzoquinin (PBQ) fixation upon mast cell staining was assessed by examination of 25 specimens fixed in both formaldehyde and PBQ; the mast cell counts obtained from tissue fixed in both of these solutions were compared.

Mast cells were counted using a calibrated graticule at $\times 400$ magnification. At least 10 non-overlapping high power fields of detrusor muscle were assessed by 2 observers who were unaware of the patient's identity (K.H.M., T.R.H.). Mast cells in the lamina propria were not counted, in

accordance with the diagnostic criterion of Larsen *et al.* (1982). Mast cells lying next to blood vessels in the interfascicular spaces between muscle bundles were also excluded from analysis.

Haematoxylin and eosin-stained sections were submitted to routine histological analysis to exclude carcinoma *in situ*, which may exist in such patients with chronic irritative symptoms (Utze and Zincke, 1974).

All patients gave informed consent to the study, which was approved by the hospital ethical committee.

The clinical and cystoscopic features of patients with normal and raised detrusor mast cell counts gave data which were not normally distributed. Results are therefore given as the median and the interquartile range (IQR): comparative analysis was performed using Wilcoxon rank analysis.

Results

The biopsies from 1 patient and 2 control subjects contained inadequate muscle for assessment. None of the control patients demonstrated excess mast cells in the detrusor muscle (median count 6.9 mast cells/mm², IQR 5.2–12). Eight patients with refractory instability (29%) had detrusor mast cell counts > 28/mm², consistent with the histological features of IC (Fig.).

There was no significant difference between detrusor mast cell counts obtained from tissue fixed in PBQ or formalin as assessed by simple linear regression (PBQ fixed tissue mast cell count = $0.86 \times$ formalin fixed tissue cell count, $P = 0.0001$).

The number of voids per day and the maximum detrusor pressure during medium fill cystometry did not differ significantly between the groups, but bladder capacity under anaesthesia was smaller in those with detrusor mastocytosis ($P = 0.016$, Wilcoxon rank) (Table 1).

At cystoscopy, 5/29 patients demonstrated marked petechial haemorrhages; bladder capacity under anaesthesia was < 500 ml in 6 subjects. Four of the 5 patients with these clinical features of interstitial cystitis had markedly elevated mast cell counts (range 52–106 mast cells/mm²); the biopsy of the fifth patient contained insufficient muscle for analysis. These 5 patients were considered to have the clinical and cystoscopic criteria necessary to make a diagnosis of interstitial cystitis; the detrusor mast cell counts were revealed to the consultant in charge as confirmatory evidence of the diagnosis, and management was therefore altered in these

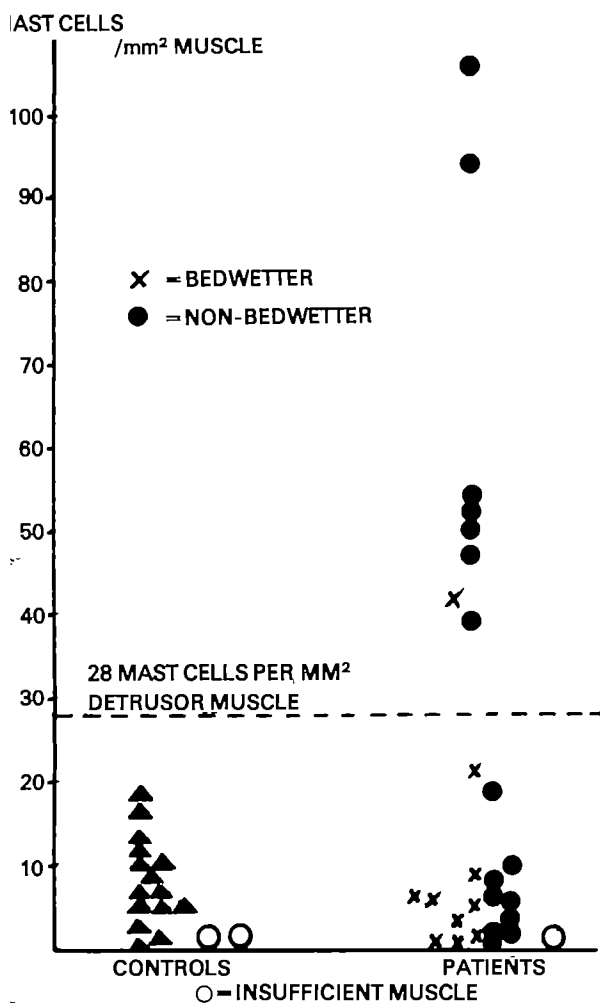


Fig. Mast cells/mm² of detrusor muscle in controls (▲) and patients (● = patients without persistent nocturnal enuresis; × = patients with nocturnal enuresis beyond age 6). ○ = specimens containing <10 high power fields of muscle, insufficient for analysis.

patients. Table 2 shows the treatments given and the subjective response obtained (subjectively successful treatments were generally accompanied by objectively demonstrated improvement in frequency volume chart parameters).

Of the 20 refractory patients with normal mast cell counts, 11 had a history of prolonged childhood bedwetting. In contrast, only 1 of the 8 patients with a raised detrusor mast cell count had a history of prolonged nocturnal enuresis.

Discussion

Idiopathic detrusor instability has previously been considered a homogeneous clinical entity. Several workers have suggested that it may be psychosomatic in origin; little search has been made for morphological abnormalities which might play a role in the aetiology of this condition. The concept that there may be a clinical spectrum of detrusor instability which could overlap with other lower tract disorders such as interstitial cystitis has not previously been investigated.

In the present selected group of 28 women with idiopathic instability who failed to respond to anticholinergic drugs, a substantial proportion (29%) had mast cell counts >28/mm² of detrusor muscle. We did not consider this histological finding to be sufficient grounds upon which to alter management, unless the clinical and cystoscopic features of interstitial cystitis were also present. This occurred in 5/28 cases (18%); the resultant alteration in management appeared clinically successful.

These findings suggest that the diagnosis of interstitial cystitis should be considered in patients with refractory detrusor instability. Refill cystoscopy to detect petechial haemorrhages, together with quantitative mast cell analysis of bladder biopsies, may be useful when anticholinergics and training have failed, since alternative treatment for interstitial cystitis may be beneficial.

Regardless of the therapeutic implications of these findings, the results may shed some light upon the aetiology of refractory idiopathic detrusor instability. Since histamine-evoked detrusor contractions are known to be atropine-resistant, it follows that patients with detrusor instability and "detrusor mastocytosis" could be unresponsive to anticholinergic drugs.

The striking trend seen in relation to persistent childhood bedwetting suggests that there may be 2 aetiological subgroups within this condition—one "acquired" and the other "congenital"—as mentioned by Gibbon *et al.* (1973) and Holmes *et al.* (1983). As research into the cause of idiopathic instability proceeds, we suggest that data should be analysed according to the presence or absence of prolonged nocturnal enuresis, in order to strengthen or refute this concept.

Finally, we believe that the relationship between mast cell numbers, histamine release and detrusor contractility should be further investigated in patients with intractable "idiopathic" detrusor instability.

Table 1 Clinical, Cystoscopic and Histological Features of Instability Patients with Normal and Raised Detrusor Mast Cell Counts

	Normal mast cell count (n=20) Median (Interquartile range)	Raised mast cell count (n=8) Median (Interquartile range)
Age (years)	49 (41–57)	50 (38–59)
Number of voids/day	15 (13–16)	12.5 (9–18)
Maximum detrusor pressure (cm H ₂ O)	30 (22–60)	32.5 (26–82)
Bladder capacity under anaesthesia (ml)	725 (650–885)	475 (360–812)
Mast cell count (/mm ² detrusor)	6.3 (3.5–10.4)	51.4 (43–84)
No. of patients with capacity under general anaesthesia < 500 ml	0	6
No. of patients with frank petechial haemorrhages	0	5

Table 2 Response to Treatment for IC in Detrusor Instability Patients with Cystoscopic and Histological Features of IC

Patient no.	Treatment	Response
1	DMSO/PP instillation	Transient relief
1	Na cromoglycate	Symptoms resolved
2	DMSO/PP	Marked relief
3	DMSO/PP	Moderate relief
4	Na cromoglycate	Moderate relief
5	DMSO/PP	Marked relief

Acknowledgements

Kate H. Moore acknowledges the financial support of the University of Liverpool Research and Development Fund. Work carried out during this study led to the submission of a Doctoral Thesis by Kate H. Moore to the Faculty of Medicine, University of Liverpool (1991).

References

- Ambache, H. and Zar, M. A. (1970). Non-cholinergic transmission by post-ganglionic motor neurones in the mammalian bladder. *J. Physiol.*, **210**, 761–783.
- Felth, J. T., Perez-Marrero, R. and Emerson, L. E. (1987). Increased mast cells of the bladder in suspected cases of interstitial cystitis. *J. Urol.*, **138**, 42–43.
- Frazer, M. I. (1988). *Mast Cells in the Hypersensitive Bladders of Females*. M.D. Thesis, University of Liverpool.
- Frewen, W. K. (1978). An objective assessment of the unstable bladder of psychosomatic origin. *Br. J. Urol.*, **50**, 246–249.
- George, N. J. R. (1986). The hypersensitive disorders of micturition. In *Sensory Disorders of the Bladder and Urethra*, ed. George, N. J. R. and Gosling, J. A. Pp.4. Berlin: Springer-Verlag.
- Gibbon, N. O. K., Jameson, R. M., Heal, M. R. et al. (1973). Transection of the bladder wall for adult enuresis and allied conditions. *Br. J. Urol.*, **45**, 306–309.
- Hald, T. and Holm-Bentzen, M. (1986). Clinical symptom complex. In *Sensory Disorders of the Bladder and Urethra*, ed. George, N. J. R. and Gosling, J. A. Pp.56. Berlin: Springer-Verlag.
- Holmes, D. M., Stone, A. R., Barry, P. R. et al. (1983). Bladder training—3 years on. *Br. J. Urol.*, **55**, 660–664.
- Kastrup, J., Hald, T., Larsen, S. et al. (1983). Histamine content and mast cell count of detrusor muscle in patients with interstitial cystitis and other types of chronic cystitis. *Br. J. Urol.*, **55**, 495–500.
- Larsen, S., Thompson, S. A., Hald, T. et al. (1982). Mast cells in interstitial cystitis. *Br. J. Urol.*, **54**, 283–286.
- Leder, L. D. (1970). Diagnostic experiences with the naphthol AS- χ chloroacetate esterase reaction. *Blut*, **21**, 1–8.
- Macartley, A. J., Stern, R. S., Holmes, D. M. et al. (1987). Micturition and the mind. *Br. Med. J.*, **294**, 540–543.
- Messing, E. M. (1987). The diagnosis of interstitial cystitis. *Urology (Suppl.)*, **29**, 4–7.
- Moore, K. H. and Sutherland, J. R. (1990). Response to treatment of detrusor instability in relation to psychoneurotic score. *Br. J. Urol.*, **66**, 486–490.
- Moore, K. H., Vallant, C., Nemeth, J. et al. (1991). Vaso-active intestinal polypeptide in refractory detrusor instability. *Neuro-urol. Urodynam.*, **10**, 330–331.
- Morrison, L. M., Eadie, A. S., McAlister, A. et al. (1986). Personality testing in 226 patients with urinary incontinence. *Br. J. Urol.*, **58**, 387–389.
- Norton, L. A., Bhat, A. V. and Stanton, S. L. (1990). Psychiatric aspects of urinary incontinence in women attending an out-patient urodynamic clinic. *Br. Med. J.*, **301**, 271–272.
- Parkit, D. E., Davis, J. A. and Symonds, R. P. (1988). Urodynamic findings following radiotherapy. *Br. J. Urol.*, **61**, 213–217.
- Perez-Marrero, R., Emerson, L. and Juma, S. (1987). Urodynamic studies in interstitial cystitis. *Urology (Suppl.)*, **29**, 27–30.
- Rubenstein, R. A., Fisher, A. and Cohen, S. (1985). Antihistaminic properties of AF-14, an experimental quinuclidine derivative: discrimination between two histaminergic sites in both guinea-pig ileum and bladder. *Eur. J. Pharmacol.*, **118**, 263–271.
- Rubenstein, R., Nissenkorn, I. and Cohen, S. (1986). Histamine-mediated release of acetylcholine in human bladder detrusor muscle. In *Proceedings of the International Continence Society Meeting, Boston*. Pp. 166–168.
- Todd, J. K. and Mack, A. J. (1969). A study of human detrusor muscle. *Br. J. Urol.*, **41**, 448–454.
- Utze, D. C. and Zincke, H. (1974). The masquerade of bladder cancer *in situ* as interstitial cystitis. *J. Urol.*, **111**, 160–161.

The Authors

Kate H. Moore, MRCOG, FRACOG, formerly Lecturer in Obstetrics and Gynaecology, University of Liverpool. Now Senior Lecturer, University Department of Obstetrics and Gynaecology, University of New South Wales, Sydney, Australia.

P. Nickson, Senior Medical Laboratory Scientific Officer, Department of Obstetrics and Gynaecology.

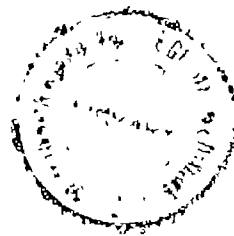
D. H. Richmond, MD, MRCOG, Senior Lecturer, Department of Obstetrics and Gynaecology.

J. R. Sutherst, MD, FRCOG, Honorary Director, Gynaecological Urodynamics Unit.

P. R. Manasse, Obstetric Statistician

T. R. Helliwell, MRCPATH, Senior Lecturer, Department of Pathology.

Requests for reprints to: Kate H. Moore, Department of Obstetrics and Gynaecology, St George Hospital, Belgrave Street, Kogarah, NSW 2217, Australia.



Electromyographic Abnormalities in the Urethral and Anal Sphincters of Women with Idiopathic Retention of Urine

R. J. WEBB, P. R. W. FAWCETT and D. E. NEAL

Department of Urology, Freeman Hospital; Department of Clinical Neurophysiology, The General Hospital; University Department of Surgery, University of Newcastle upon Tyne

Summary—Previous concentric needle studies of the urethral sphincter in women with idiopathic urinary retention have found evidence of denervation and reinnervation as well as abnormal patterns of muscle fibre discharge—complex repetitive discharges (CRDs). In order to test the hypothesis that these abnormalities represented a more widespread disease process of pelvic floor function, we carried out an electromyographic (EMG) study of both anal and urethral sphincters in 18 women with idiopathic urinary retention.

The urethral sphincter EMG was abnormal in 15 patients. These abnormalities included polyphasic and long duration potentials. Complex repetitive discharges were identified in 8 women. However, abnormalities of the anal sphincter were found in 14 of the 15 patients with abnormal urethral sphincter EMGs, polyphasic and abnormally long duration potentials being found in the anal sphincters of all 14 patients. In addition, 7 of the 8 women who had complex repetitive discharges in the urethral sphincters had similar complex repetitive discharges in their anal sphincters. Women with complex repetitive discharges had a significantly greater proportion of abnormal potentials than women with no such repetitive discharges.

These results support the previous findings of electromyographic urethral sphincter abnormalities in women with idiopathic urinary retention, but also suggest that these abnormalities reflect a widespread disease process involving the pelvic floor in such patients.

Effective voiding of the normal urinary bladder during micturition is dependent upon a co-ordinated relaxation of the striated sphincter muscle of the urethra which precedes and accompanies contraction of the detrusor muscle. Mechanical obstruction to voiding in the ageing male is usually associated with benign prostatic hypertrophy and can result in failure of the detrusor muscle, presenting as acute or chronic retention of urine (Neal, 1991). Retention of urine in women, on the other hand, rarely has a simple mechanical or an overtly neuropathic aetiology. In the past, many women with chronic painless distension of the bladder were thought to have either a psychological cause or some unexplained disorder causing degeneration of the detrusor muscle.

More recently, it has been shown by Fowler and Kirby (1985, 1986) that many of these women have abnormal electromyographic activity in the striated muscle of the urethra. In a study of 48 women, one-third had evidence of denervation, and in a further 40% a particular type of abnormality was found which was termed decelerating bursts and complex repetitive discharges (DBs and CRDs) (Fowler and Kirby, 1986). It was also suggested that this type of abnormality might be associated with endocrine dysfunction and polycystic ovaries (Fowler *et al.*, 1988) and that the neuromuscular defect might be brought about by a relative progesterone deficiency. The muscles of the pelvic floor, the pelvic viscera and the associated sphincters share several common features in terms of structure and innervation. For example, a significant proportion of women with stress urinary incontinence have symptoms of faecal incontinence and associated neurophysiological

abnormalities; similarly, a proportion of women with faecal incontinence have abnormal urethral function (Snooks and Swash, 1984). It has been proposed that damage to the innervation of the pelvic floor during obstetric delivery is the common cause of these abnormalities. We carried out the present study to determine whether abnormalities in the urethral sphincter of patients with idiopathic urinary retention could also be found in the anal sphincter, and to test the hypothesis that such dysfunction might reflect a more widespread disorder of the whole pelvic floor.

Patients and Methods

Eighteen women (aged 47 ± 17 years) with idiopathic urinary retention were studied. None had overt neuropathy. Four women had undergone pelvic surgery (1 hysterectomy, 1 salpingo-oophorectomy, 3 dilatation and curettage). None of the patients who had undergone previous pelvic surgery had signs on video-urodynamic testing of damage to the pelvic autonomic plexus as demonstrated by impaired bladder compliance during bladder filling (Neal, 1984). At the time of the EMG investigation, all 18 patients were performing clean intermittent self-catheterisation (for a median of 27 months; range 0–84). Ten women had presented with acute on chronic retention. The remainder had presented with urinary frequency and difficulty in initiating voiding accompanied by the finding of a large volume of residual urine and palpable bladder; 5 patients also complained of incontinence. Eight patients had experienced recurrent urinary tract infections. As is commonly the case, all patients had undergone urethral dilatation (median 2) and 13 had undergone at least 1 urethrotomy in the hope of improving bladder emptying. Temporary improvement in voiding was reported in 12 of 18 patients after their first urethral dilatation. Three patients complained of constipation and 1 of faecal incontinence. Four women had undergone forceps deliveries.

Video-urodynamic study

All patients had been catheterised or were practising clean intermittent self-catheterisation (CISC) at the time of the study. They were catheterised with a 10 and a 6F catheter, the former being used to fill the bladder with dilute contrast medium at room temperature at a rate of 100 ml/min; the other, being filled with saline, was attached to an external pressure transducer levelled at the level of the symphysis pubis and used to measure bladder

pressure. Another fine catheter, its end covered by a vented finger cot, was inserted into the rectum and used to estimate intra-abdominal pressure. This pressure was subtracted from bladder pressure electronically to give an estimate of detrusor pressure. The bladder was filled until the patients stated they were full, when they were asked to pass urine into a flow meter. At the conclusion of voiding, residual urine was measured using a Kretz Combison ultrasound machine.

Electromyography

EMG of the striated muscle of the external urethral sphincter was performed as follows. The patient lay with her hips flexed and abducted and after cleansing of the skin with a proprietary skin preparation a Medelec concentric needle (length 3.0 cm, tip diameter 0.45 mm) was inserted lateral to the external urethral meatus and guided into the sphincter by a combination of palpation *per vaginam* and by means of the audio signal obtained from the Medelec Neurolog system. When correct needle placement was obtained the sweep speed of the oscilloscope was increased and a delay line with signal triggering was used, allowing visualisation of individual motor units. An average of 20 ± 4 motor units were identified and analysed and this required at least 2 separate needle insertions. All data were stored on a TEAC digital audio recorder in order to facilitate later playback and analysis. A similar method was used for EMG of the anal sphincter, which was carried out after needle insertion on both sides.

Abnormal values were defined as follows for the urethral sphincter (Chantraine, 1973). A long duration potential was defined as longer than 6 ms and a polyphasic potential as more than 4 phases of voltages greater than 100 μ V. For the anal sphincter, an abnormal potential was one which lasted longer than 8 ms (Chantraine, 1973). Complex repetitive discharges were defined according to the criteria described by Fowler and Kirby (1985); they had to be widespread, spontaneous, not associated only with needle insertion and identified in more than one site. Overall, the EMG was defined as abnormal if more than 25% of the potentials were polyphasic or abnormally long (Chantraine, 1973; Fowler and Kirby, 1985; Fowler *et al.*, 1985). Instability of potentials was defined if the variability in onset of a defined later peak exceeded 80 μ s. The results are presented as means ± 1 standard deviation. Statistical analysis was performed by techniques suitable for non-parametric data, using the χ^2 test with correction for

continuity and the Mann-Whitney test; a *P* value of 0.05 was taken as statistically significant on 2-tailed testing.

Results

Video-urodynamic study

The mean pressure rise during filling was 9 ± 2 cm H₂O (range 4–12), and after drainage of residual urine (performed some days previously) the mean cystometric bladder capacity was 207 ± 87 ml (range 90–490). Thirteen patients failed to generate any detrusor voiding contraction; in the remaining 5 patients the pressure during attempted voiding ranged from 16 to 26 cm H₂O. The residual urine measured at completion of the urodynamic study was 459 ± 142 ml, but had been considerably more than this at the time of original catheterisation. Four patients had evidence of mild genuine stress incontinence on video-urodynamic study, with the volume leaked ranging from 5 to 10 ml.

Electromyography of urethral sphincter

Abnormalities of the urethral sphincter were found in 15 patients. The most common abnormality was an excess of polyphasic potentials and abnormally long duration potentials. Complex repetitive discharges were identified in 8 patients. CRDs were not identified in the 4 women with mild genuine stress incontinence. The mean proportion of polyphasic potentials in the group without CRDs ($34 \pm 26\%$) was significantly smaller than in the group with CRDs (excluding the CRDs themselves: $50 \pm 20\%$; $P < 0.02$). The mean duration of potentials was shorter in the group without CRDs (6.75 ± 4 ms) compared with the group with CRDs, but this did not reach statistical significance (9.0 ± 2.4 ms; $P < 0.06$). Of the 8 women with CRDs, 7 had an overall abnormal EMG because of polyphasic and long duration potentials (excluding the CRDs themselves). Only 1 woman had CRDs superimposed on an otherwise normal EMG.

Of the 10 patients without CRDs, instability of potentials was observed in 2, both of whom had an abnormal EMG. Of the 8 patients with CRDs, 5 had unstable potentials and instability was observed in both CRDs and polyphasic potentials in 3 of them. This suggested that the disease process was still ongoing.

Electromyography of the anal sphincter

The mean amplitude of the potentials in the anal sphincter (927 ± 240 μ V) was significantly greater than those of the urethral sphincter (325 ± 96 μ V; $P < 0.001$). Abnormalities of the anal sphincter

were found in 14 patients. Once again, the most common were polyphasic and abnormally long duration potentials. Complex repetitive discharges were identified in 7 patients. All 7 patients with CRDs in the anal sphincter had similar abnormalities in the urethral sphincter. The remaining patient with CRDs in the urethral sphincter had no such abnormality in an otherwise normal anal sphincter. The mean proportion of polyphasic potentials in the group without CRDs ($29 \pm 28\%$) was significantly smaller than in the group with CRDs (41 ± 25 ; $P < 0.05$). The mean duration of potentials was shorter in the group without CRDs (6.1 ± 3 ms) compared with the group with CRDs, but this did not reach statistical significance (7.3 ± 2 ms; $P < 0.08$). Of the 7 women with CRDs, all had an abnormal EMG because of polyphasic potentials and abnormally long duration potentials.

Of the 11 patients without CRDs, 2 had unstable potentials; both had an abnormal EMG with polyphasic potentials and 1 also had unstable potentials observed on the urethral EMG. Of the 7 patients with CRDs in the anal sphincter, 5 had unstable potentials and, of these 5 patients, instability was observed in both CRDs and in polyphasic potentials in 4.

Discussion

This study supports the findings of previous authors that electromyographic abnormalities are common in the urethral sphincter of women with otherwise unexplained urinary retention (Fowler and Kirby, 1985, 1986; Fowler *et al.*, 1985, 1988) or other symptoms of urgency, frequency and genuine stress incontinence (Butler, 1979). The present study also reports that similar abnormalities are frequently found in the anal sphincter of such patients, suggesting that they have a more widespread disorder of the pelvic floor than had been thought previously.

It has been suggested that complex repetitive discharges are the result of ephaptic transmission between muscle fibres (Fowler *et al.*, 1985). The origin of this activity remains speculative; previous authors have felt that a relative progesterone deficiency may be the cause. Our finding that most of the patients with CRDs also have abnormalities suggestive of denervation and reinnervation suggests that a more widespread disorder of pelvic floor innervation is present. Our finding that CRDs were associated with a greater number of abnormal patterns of muscle fibre discharge suggests that women with the most severe denervation might be

at higher risk of developing CRDs. This raises the question of whether CRDs are associated specifically with urinary retention or whether denervation of the sphincter is the primary abnormality, with a later development of CRDs owing to some other cause.

The anatomy of the musculature of the pelvic floor, its sphincters and their innervation has been clarified. It is now known that the puborectalis muscle is usually supplied directly by a branch of the sacral plexus situated above the pelvic floor and not, as previously thought, by the internal pudendal nerve. It is also clear that the striated sphincter muscle of the urethra is an integral part of the urethra distinct from the pelvic floor, receiving its somatic innervation via the pelvic autonomic plexus. The extrinsic peri-urethral striated muscle, on the other hand, is part of the pelvic floor, receiving its nerve supply via the pudendal nerve and by direct branches entering from above the pelvic floor, whereas the anal sphincters proper receive their innervation via the pudendal nerve (Lawson, 1974). It is therefore not surprising on these grounds that disorders affecting the urethral sphincter also tend to affect the anal sphincter (Snooks and Swash, 1984).

It has been suggested that the presence of CRDs is particularly associated with idiopathic urinary retention in women; the presence of similar abnormalities in women with other lower urinary tract symptoms (Fowler and Kirby, 1986) has been suggested to be a precursor of later detrusor decompensation and therefore of urinary retention, although in one study the abnormalities were associated with genuine stress incontinence (Butler, 1979), making this suggestion less likely to be correct. It is suggested that these abnormal repetitive discharges impede sphincter relaxation, resulting in chronic outflow obstruction which in turn damages the smooth muscle of the detrusor (Fowler and Kirby, 1986). However, it should be noted that the incidence of this EMG abnormality in patients with retention was only about 44% in our study—a similar incidence to that observed previously by Fowler (40%). Why the remaining patients should have retention of urine remains unexplained by our study. On the other hand, all reported patients with this type of activity are symptomatic (Fowler *et al.*, 1985). Other EMG abnormalities, including changes consistent with denervation and reinnervation, were found frequently in our patients (83%), as in previous series; one possible explanation is that such abnormalities are also found frequently with ageing and in women with genuine stress

incontinence, raising the question of whether these changes were associated with idiopathic retention of urine in a non-specific way. The other unexplained finding is why the presence of CRDs in the anal sphincter is only rarely associated with lower gastrointestinal symptoms. The present study suggests that women with otherwise unexplained urinary retention commonly have EMG abnormalities in the urethral sphincter, but also often have similar abnormalities in the anal sphincter, reflecting a widespread disease process involving the whole pelvic floor.

References

- Butler, W. J. (1979). Pseudomyotonia of the periurethral sphincter in women with urinary incontinence. *J. Urol.*, **122**, 838–840.
- Chantraine, A. (1973). EMG of the anal and urethral sphincters. In *New Developments in Electromyography and Clinical Neurophysiology*, ed. Desmedt, J. E. Volume 2. Pp. 421–432. Basel: Karger.
- Fowler, C. J. and Kirby, R. S. (1985). Abnormal electromyographic activity (decelerating burst and complex repetitive discharges) in the striated muscle of the urethral sphincter in 5 women with persisting urinary retention. *Br. J. Urol.*, **57**, 67–70.
- Fowler, C. J. and Kirby, R. S. (1986). Electromyography of urethral sphincter in women with urinary retention. *Lancet*, **I**, 1455–1457.
- Fowler, C. J., Kirby, R. S. and Harrison, M. J. G. (1985). Decelerating burst and complex repetitive discharges in the striated muscle of the urethral sphincter, associated with urinary retention in women. *J. Neurol. Neurosurg. Psychiatry*, **48**, 1004–1009.
- Fowler, C. J., Christmas, T. J., Chapple, C. R. *et al.* (1988). Abnormal electromyographic activity of the urethral sphincter, voiding dysfunction and polycystic ovaries: a new syndrome. *Br. Med. J.*, **297**, 1436–1438.
- Lawson, J. O. N. (1974). Pelvic anatomy. 2. Anal canal and associated sphincters. *Ann. R. Coll. Surg. Engl.*, **54**, 288–300.
- Neal, D. E. (1984). The effects on pelvic visceral function of anal sphincter ablating and anal sphincter saving preserving operations for cancer of the lower part of the rectum and for benign disease. *Ann. R. Coll. Surg. Engl.*, **66**, 7–13.
- Neal, D. E. (1991). Bladder outflow obstruction and the outcome of surgery. In *Recent Advances in Urology/Andrology*, No. 5, ed. Hendry, W. F. Chapter 10. Pp. 149–165. Edinburgh: Churchill Livingstone.
- Snooks, S. J. and Swash, M. (1984). Abnormalities of the urethral striated sphincter musculature in incontinence. *Br. J. Urol.*, **56**, 401–405.

The Authors

- R. J. Webb, FRCS, formerly Research Registrar, Department of Urology, Freeman Hospital. Now Senior Urological Registrar, West Midlands Hospitals.
- P. R. W. Fawcett, MD, BSc, MRCP, Consultant Neurophysiologist, Newcastle General Hospital.
- D. E. Neal, FRCS, MS, BSc, Senior Lecturer, University Department of Surgery and Consultant Urologist, Department of Urology, Freeman Hospital.

Requests for reprints to: D. E. Neal, Department of Urology, Freeman Hospital, Newcastle upon Tyne NE7 7DN.

Continent Urinary Diversion Using an Artificial Urinary Sphincter

P. MITROFANOFF, O. BONNET, M. P. ANNOOT, F. BAWAB and P. GRISE

Paediatric Surgery Clinic and Department of Urology, Centre Hospitalier Universitaire, Rouen, France

Summary—We report a new and simplified method of continent urinary diversion employing a modified AMS 800 artificial urinary sphincter (AUS). Our aim in using this artificial valve is to make a stoma continent, while allowing intermittent catheterisation. The AMS 800 pump is replaced by a subcutaneous injection port. This allows, by direct puncture, the accurate setting of the closing pressure by varying the volume of the intra-prosthetic liquid, with subsequent adjustment of this pressure as necessary. The cuff is placed on the subcutaneous part of the intestinal loop diversion. The pressure-regulating balloon is implanted within the area of abdominal pressure, retroperitoneally.

After first confirming the efficacy of the system in 3 dogs, the device was placed in 2 patients. The first had a neuropathic bladder treated initially by enterocystoplasty with an appendicocutaneous stoma. Secondary leakage was subsequently controlled by placement of the device, with continuing excellent results at 32 months. The second patient was a girl in whom a urogenital rhabdomyosarcoma had been treated by anterior exenteration, radiotherapy and a sigmoid conduit diversion. This was subsequently converted to a continent reservoir by simple augmentation of the conduit and placement of the device, with a good result being maintained after a follow-up of 20 months.

These two cases illustrate the best indications for this procedure, namely primary or secondary leakage from a supposedly continent urinary diversion, and conversion of a freely draining conduit into a continent reservoir.

Although long-term results are still pending, our experience thus far encourages us to recommend this technique as a simple means of achieving a continent urinary diversion.

Various methods of continent urinary diversion have been described in the past few years. All have insisted on the use of a low pressure reservoir which is emptied by catheterisation of the continent stoma. Whatever the method used, the valve system may fail. We propose a new simple method.

Materials and Methods

The artificial valve

Three elements are connected to one another by a Y-shaped tube. Two of these elements are derived from the AMS 800 artificial sphincter: (1) an

occlusive cuff placed subcutaneously on the stoma to provide continence; (2) a pressure regulating balloon implanted within the abdomen, so that any increase in intra-abdominal pressure is transmitted to the cuff via the connecting tubing.

The third element is a subcutaneous injection port which allows accurate setting of the closing pressure at a level just sufficient to ensure continence. Subsequent adjustments to the pressure are possible in case of secondary loss of continence.

This system does not require a deactivation pump. It allows catheterisation of the stoma and provides continence (Fig. 1).

In vitro study

The behaviour of this artificial valve was studied during intraprosthetic liquid filling in an open

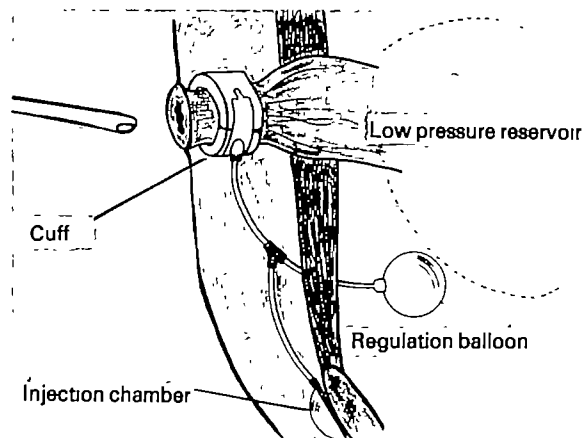


Fig. 1 Position of artificial sphincter to create continent urinary diversion.

enclosure. We then studied it after placing the cuff around an isolated loop of human intestine.

This analysis confirmed that the curve of effective pressure variations with respect to the volume of liquid in the prosthesis was S-shaped (Fig. 2), the slope of which depended on the compliance of the regulating balloon. In the sphincter models tested there was a margin of variation of intraprosthetic volume of 3 to 5 ml between the lowest and the highest range of effective pressure.

Animal study

This system was tested in 3 dogs (15 to 20 kg beagles) by performing isoperistaltic transileal cystostomies. The cuff was placed in the subcutaneous tissue, the balloon between the abdominal

muscles and peritoneum and the subcutaneous port of injection overlying the anterior iliac spine. The pressure under the cuff was fixed at 40 cm H₂O. The dogs were monitored for 6 months with general anaesthesia every 2 months, for manometric studies of the diversion, X-ray studies with retrograde opacification through the stoma and anatomical dissection during the final examination.

The post-operative course was uncomplicated. Clinical examination showed that in all cases the stoma remained correctly vascularised with no leakage either at rest or on effort. Catheterisation through the valve remained easy.

We studied the effect of abdominal excess pressure by applying sudden external pressure to the animal's abdomen. Continence was complete, the valve being able to prevent leakage by transmitting the excess pressure via the regulating balloon. However, clamping the tubing between cuff and balloon stopped the transmission of excess pressure and, as with the removal of the liquid from the prosthesis, suppressed continence.

Cystography showed arrest of the contrast medium at the valve level.

Finally, anatomical examination showed a fine fibrous capsule around all of the prosthetic elements and atrophy of the tissue under the cuff without any histological ischaemic lesion.

These satisfactory results encouraged us to apply this method in humans.

Case Reports

Case 1. A boy with a meningocele of the lumbar spine was initially treated by an appendicocutaneous stoma and closure of the bladder neck at 11 years of age. This worked well for 4 years but vesical hypertonicity led to bladder neck recanalisation and upper tract dilatation, which required an enterocystoplasty. Leakage reappeared through the appendicocutaneous stoma which had thus far been continent. Exploration showed an alteration in the submucosal course of the appendix, probably caused post-operatively by a balloon catheter. An attempt to reconstruct the submucosal tunnel failed. The intravenous urogram was normal and vesical capacity good.

A 4.5-cm AMS 800 cuff was placed around the appendix in a subcutaneous site. A balloon of 51–60 cm H₂O was placed between the muscle and the peritoneum, and the subcutaneous port was implanted on the external surface of the iliac bone. The system was activated 8 days after the operation by an injection of 16 ml with 75 cm H₂O pressure under the cuff, providing good continence (Fig. 3).

Twenty-seven months later, cutaneous ulceration occurred opposite the subcutaneous port. The port was then replaced in a safer site. The system was reactivated

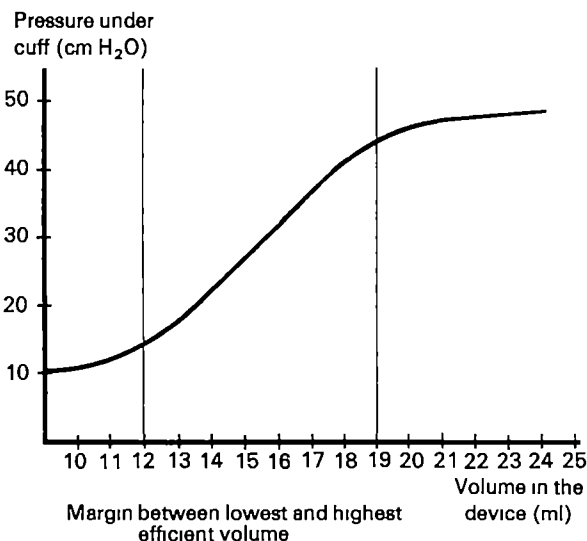


Fig. 2 Relationship between pressure under cuff and volume in the prosthesis.

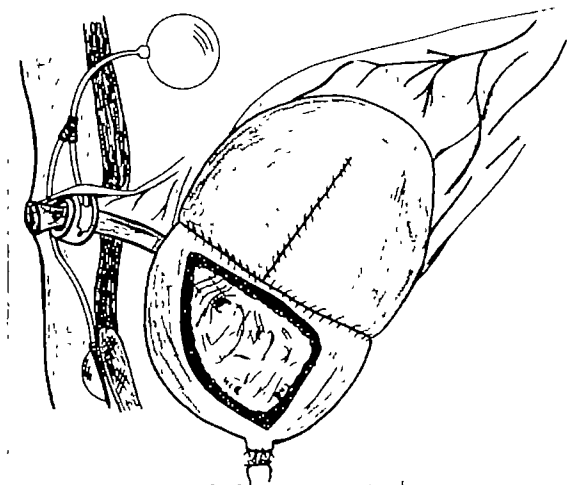


Fig. 3 Artificial sphincter and appendico-cutaneous stoma.

according to the same parameters as before and good results were achieved. The AUS has now been in use for 32 months, 5 months of which have been spent in the new injection site. The intravenous urogram is still normal.

Case 2. This second patient was a girl who had a urogenital rhabdomyosarcoma treated by anterior exenteration in the first years of her life. Initially she had a colonic urinary diversion with a poor result regarding anal continence, probably due to radiotherapy. A cutaneous sigmoid diversion was performed but at 18 years of age she asked for a diversion without an external device.

The upper urinary tract was in good condition and there was no ureteric reflux. The situation was therefore ideal for the creation of a continent reservoir, preserving the stoma and sigmoid-ureteric junction.

A reservoir was created using a detubularised ileal loop which was then connected to the sigmoid conduit. A few weeks later an AMS 800 AUS with a 4.5 cm cuff and 51–60 cm regulating balloon was inserted (Fig. 4). Eight days later the system was activated via the subcutaneous port. A 9-ml injection first provided a pressure of 50 cm H₂O under the cuff, with initial good continence. Two months later, leakage occurred and the cuff pressure fell to 35 cm H₂O. An injection of 3 ml caused the pressure to rise to 60 cm. Continence returned to a satisfactory level and remained at 62 cm H₂O, but it started to drop again a few months later. A further injection of 1 ml returned the cuff pressure to 90 cm H₂O and all leakage disappeared. The situation has remained stable for 22 months since implantation of the AUS and 16 months since the last injection. An intravenous urogram remains stable.

Discussion

The 3 parts of this study have shown that continence can be achieved down-stream from a low pressure

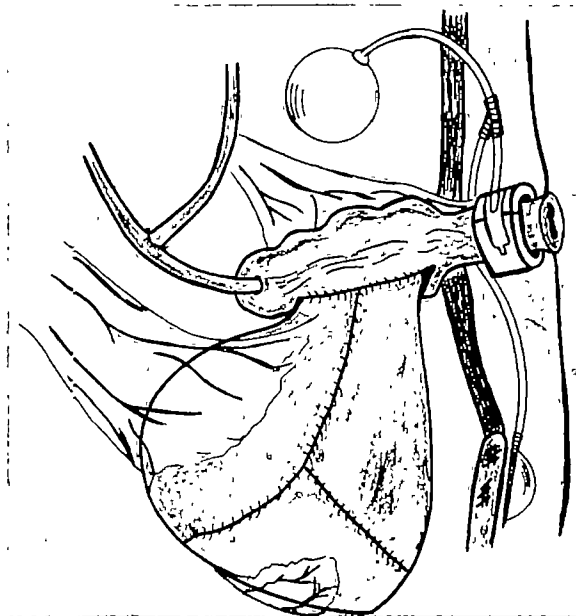


Fig. 4 Artificial sphincter, sigmoid conduit and ileal reservoir.

reservoir by a prosthetic valve. The device we use does not require the pump of the AMS 800, which is probably the weak part of the device.

The remaining uncertainty as to the future of such a system involves the tolerance of the intestinal tissue to continuous pressure under the cuff, and persistence of its efficacy.

Animal application

Delaney *et al.* (1974) demonstrated experimentally that, in a dog's bowel, there is no vascular modification to a cuff pressure of 125 cm H₂O.

In 1985, Engelman *et al.* observed necrosis under the cuff of an AMS 800 AUS, above 100 cm H₂O in the intestinal loop of a rabbit. Otherwise tolerance was good and histological examination revealed a fine fibrous capsule around the cuff and the bowel beneath the cuff.

Clinical applications

Clinical applications are few. In 1987 Burbige *et al.* reported 9 reconstructions of the lower urinary tract in cases of vesical exstrophy, using an AUS. In 8 cases, urinary leakage appeared 6 to 10 months post-operatively. Loss of continence was linked to atrophy of the tissue under the cuff. The situation required a further procedure to replace the cuff with another one of appropriate size.

Light (1989) reported 4 cases involving placement

of an AUS around the bowel, replacing the urethra. In one case, erosion appeared under the cuff at a pressure of 80 to 90 cm H₂O. In 2 cases the cuff was replaced by a smaller one.

Weston *et al.* (1991) also used an AUS around bowel in 8 patients, 6 times after an enterocystoplasty and twice around a stoma. The sphincter was efficient in 7 cases, but 1 patient developed leakage on physical effort. In 1 case erosion under the cuff required removal of the sphincter.

These reports, together with our experimental study, confirm the efficacy of an AUS around a stoma to provide continence to a low pressure reservoir. However, there is a relatively narrow margin between the low pressures providing continence and excessive pressure involving ischaemia and erosion. Moreover, a few studies have revealed atrophy of the bowel under the cuff, which was responsible for the loss of efficacy of the system.

Under these conditions, the device with a subcutaneous port of injection allows the volume to be regulated and ensures that pressure is just sufficient to provide continence. We recommend that the system be activated 8 days after placement, when the oedema under the cuff has disappeared. When intestinal atrophy occurs, with loss of continence, a new pressure-controlled injection is possible.

A further observation is the appearance of a fine fibrous capsule around the prosthesis. It is possible that this capsule was responsible for a loss of compliance of the regulating balloon. We have noted that reinjection of a very small amount of liquid into the device (1 or 2 ml) results in a pressure increase of 30 to 50 cm H₂O.

Another advantage of our system is the elimination of the AMS 800 pump. Although the mechanism has become reliable, it may occasionally fail. On the other hand, our subcutaneous injection port was responsible, in 1 of 2 cases, for cutaneous ulceration which required placement of another port in a different site. Initially, it was implanted in contact with the ilium, allowing easy percutaneous injections, but when placed between skin and muscle, stability is adequate. One must, however, choose a suitable location on the abdominal wall.

Thus the resistance of such a system is comparable to the resistance of an AUS in its usual form. It does not seem that frequent use of the catheter leads to ulceration of the mucosa under the cuff. It is still too soon to know if muscular atrophy observed under the cuff is likely to increase, but our impression is that sooner or later a state of equilibrium is reached. In our 2 patients, the

situation has been stable without injections for 32 months in 1 case and 16 months in the other.

A great advantage of this type of AUS is the simplicity of implantation. In accordance with other authors, we suggest that placement of the device be a separate procedure from creation of the stoma and the reservoir. This operating sequence is straightforward and mainly subcutaneous, apart from implantation of the regulating balloon, which is placed in a subperitoneal location through a muscle split.

The system should be activated about 8 days after implantation, when oedema has disappeared; the injection must be done with close surveillance of the cuff pressure, so that continence is achieved with the lowest pressure possible.

Our 2 patients illustrate the best indications for implantation of the modified AUS:

- (1) The development of leakage with a low pressure reservoir in a supposedly continent urinary diversion where the intestinal valve (or appendix) has lost its efficacy.
- (2) Transformation of a direct cutaneous drainage system into a continent reservoir. In this case, stoma and ureteric anastomosis are already there. It is necessary to confirm the absence of reflux.

This device may have wider applications, particularly in the development of continent urinary reservoirs.

References

- Barbidge, K., Reitelman, C. and Olson, C. (1987). Complications of artificial urinary sphincter around intestinal segment in reconstructed exstrophy patients. *J. Urol.*, **138**, 1123–1125.
- Delaney, J., Broadie, T., Timm, G. *et al.* (1974). A prosthetic sphincter for the gastrointestinal tract. *J. Surg. Res.*, **16**, 204–209.
- Engelman, U. H., Felderman, T. P. and Scott, F. B. (1985). The use of A.M.S. 800 artificial sphincter for continent urinary diversion. Investigation including pressure flow study, using rabbit intestinal loops. *J. Urol.*, **134**, 183–186.
- Light, J. K. (1989). Long-term clinical results using the artificial urinary sphincter around bowel. *Br. J. Urol.*, **64**, 56–60.
- Weston, P. M. T., Morgan, J. D. T., Hussain, J. *et al.* (1991). Artificial urinary sphincters around intestinal segments—are they safe? *Br. J. Urol.*, **67**, 150–154.

The Authors

P. Mitrofanoff, MD, Professor of Paediatric Surgery, Paediatric Surgery Clinic.

O. Bonnet, MD, Urologist.

M. P. Annoot, MD, Urologist.

F. Bawab, MD, Paediatric Surgeon

P. Grise, MD, Urologist.

Requests for reprints to: P. Mitrofanoff, Clinique Chirurgicale Infantile, Centre Hospitalier Universitaire, Hôpital Charles-Nicolle, Boulevard Gambetta, 76000 Rouen, France.

The Effect of Ranitidine on Urine Mucus Concentration in Patients with Enterocystoplasty

V. K. GEORGE, J. M. GEE, M. I. WORTLEY, M. STOTT, C. G. C. GACHES and M. H. ASHKEN

Department of Urology, Norfolk and Norwich Hospital; Institute of Food Research, Norwich Laboratory, Norwich

Summary—We describe the effect of ranitidine in reducing mucus in urine in 8 patients with enterocystoplasty and present a simple technique for measuring the concentration of mucus in urine. After a 10-day course of ranitidine (300 mg daily in divided doses) the concentration of mucus had fallen significantly from an initial level of 1.38 ± 0.18 to 0.39 ± 0.04 mg/ml.

The bowel is used more frequently than ever before in all types of bladder reconstruction, such as augmentation and substitution cystoplasty (Ashken, 1982; Goldwasser and Webster, 1986). Because of its inherent capacity to produce mucus, this can predispose the urinary tract to infection and exacerbate urinary retention in a low pressure system which may also have bladder outlet obstruction. In those patients who are on clean intermittent self-catheterisation, mucus can block the catheter (Gillon and Mundy, 1989).

We describe a simple method to measure the concentration of mucus in the urine and report the effect of ranitidine on mucus production by transplanted segments of bowel in patients with an enterocystoplasty.

Patients and Methods

Ten patients, all women who had undergone enterocystoplasty in the past, were recruited for the present study and the procedure was fully explained to them. A 24-h urine sample was collected before drug treatment and again on the ninth day of a 10-day course of ranitidine, 300 mg daily in divided doses (150 mg 12-hourly). All patients were instructed to discontinue the drug if any adverse

reaction occurred. Two patients withdrew from the study after collection of the first sample.

Each 24-h urine sample was mixed by shaking to give a homogeneous suspension prior to an aliquot (10 ml) being taken for analysis. The pH of the subsample was recorded and adjusted to 4.6 with a minimal volume of hydrochloric acid (IM), then centrifuged for 10 min at 2500 rpm (Beckmann TJ-6 bench top centrifuge). The supernatant was collected and 2 ml pipetted into a pre-prepared, moist dialysis sac (dialysis tubing—Visking size 2-18/32", Medical International Ltd). The sac was closed with a further knot and suspended in a flask containing distilled water. The sample was dialysed against approximately 200 volumes of water at +5°C for 20 h, with continuous stirring. No significant change in sample volume was observed.

Aliquots of the dialysed sample, diluted as necessary, were analysed using the anthrone spectrophotometric method (Roe, 1955). Duplicate aliquots (0.5 ml) of the diluted sample were mixed with anthrone reagent (5 ml) in dry, securely stoppered tubes and transferred to a boiling water bath for 11 min. The tubes were then cooled in the dark for 20 to 30 min and the absorbance at 620 nm measured using a Pye Unicam SP 30 UV spectrophotometer (Anderson and Maclagen, 1985).

A stock solution of mucin (BDH, Poole) was prepared and a standard curve for concentrations of mucin between 0 and 5 mg/ml optical density was plotted against concentration (Fig.). The equation for the straight line portion of the standard

Based on a Poster Demonstration at the 47th Annual Meeting of the British Association of Urological Surgeons in Glasgow, June 1991

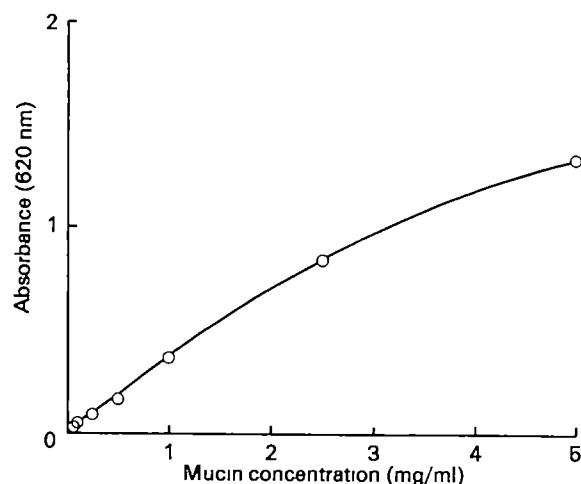


Fig. Standard curve for mucin determination using the anthrone assay.

curve was obtained by linear regression and used to calculate the concentration of mucus in the urine samples from their optical densities. The results are expressed in mg/ml. The entire procedure was validated using the stock mucin solution.

The results were analysed for significance using Student's paired *t* test.

Results

Seven of the 8 patients reported a reduction in the amount of mucus in the urine while on ranitidine. The Table gives data for mucus levels before and after treatment and shows a significant reduction in the concentration from 1.381 ± 0.183 to 0.391 ± 0.044 ($P < 0.001$). No adverse reactions were recorded and all patients tolerated the drug well.

Discussion

Mucus is a glycoprotein with a molecular weight between 2 and 20 million daltons with viscous and gel-forming properties. Of this 50 to 70% are carbohydrate units which are linked together around a central protein core. The protein core is synthesised by the rough endoplasmic reticulum of the goblet cells; glycosylation then occurs by stepwise addition of sugar moieties to the core in the smooth endoplasmic reticulum and Golgi complex. The newly formed mucus is stored in the form of vesicles prior to secretion (Allen *et al.*, 1985).

When bowel segments are used for augmentation or substitution cystoplasties they continue to produce mucus, contaminating the urine. This can

Table Concentration of Mucus in Urine (ml/ml)

Patient no.	Before treatment	After treatment
1	1.18	0.36
2	1.11	0.40
3	1.47	0.40
4	1.33	0.68
5	2.27	0.33
6	0.53	0.26
7	1.86	0.40
8	1.30	0.31
	1.38 ± 0.18	0.39 ± 0.04

$P < 0.001$.

cause voiding difficulties and predispose to retention of urine. Many workers have used a variety of methods to measure the amount of mucus *in situ* in the urine (Murray *et al.*, 1987). Attempts have been made to render the mucus soluble by using various agents, and Gillon and Mundy (1989) demonstrated that 30 ml of 20% acetylcysteine instilled into the bladder after emptying and left overnight was an effective mucolytic agent.

In this pilot study we developed a simple laboratory procedure to assess the effect of ranitidine on mucus production, showing that a marked reduction occurred while the patients with enterocystoplasty were taking the drug. It is difficult at this stage to establish the mechanism of action of ranitidine, but further studies are in progress to assess this, including biopsy of the cystoplasty before and after treatment. The present observation is, however, of significance to mucus production throughout the intestinal tract as ranitidine, an H_2 receptor blocker, is widely used in the treatment of gastric and duodenal ulcers and other upper gastrointestinal disorders.

Acknowledgements

We are grateful to Mr N. A. Green for his encouragement and valuable suggestions and thank Jenny and Daphne for their secretarial assistance.

References

- Allen, A., Cunliffe, W. J., Hunton, D. A. *et al.* (1985). Gastrointestinal mucus. *Top Gastroenterol.*, **12**, 211-224.
- Anderson, A. J. and MacLagen, N. F. (1985). Isolation and estimation of urinary mucoproteins. *Biochem. J.*, **59**, 638-644.
- Ashken, M. H. (1982). Urinary reservoirs. In *Clinical Practice in Urology. Urinary Division*. Pp 112-139. Berlin, Heidelberg, New York: Springer-Verlag.
- Gillon, G. and Mundy, A. R. (1989). The dissolution of mucus after cystoplasty. *Br. J. Urol.*, **63**, 372-374.
- Goldwasser, B. and Webster, G. D. (1986). Augmentation and substitution enterocystoplasty. *J. Urol.*, **135**, 215-220.

- Murray, K., Nurse, D. E. and Mundy, A. R. (1987). Secretomotor function of intestinal segments used in lower urinary tract reconstruction. *Br. J. Urol.*, **60**, 532-535.
- Roe, J. H. (1955). The determination of sugar in blood and spinal fluid with anthrone reagent. *J. Biol. Chem.*, **212**, 335-343.
- J. M. Gee, MIBiol, CBiol, Senior Scientific Officer, Institute of Food Research.
- G. Wortley, Assistant Scientific Officer, Institute of Food Research.
- M. Stott, MS, FRCS, Senior Registrar, Norfolk and Norwich Hospital.
- C. G. C. Gaches, MS, FRCS, Consultant Urologist.
- M. H. Ashken, MS, FRCS, Consultant Urologist

The Authors

- V. K. George, MS, FRCSI, formerly Registrar, Norfolk and Norwich Hospital. Now Registrar, Walsgrave Hospital, Coventry.
- Requests for reprints to: V. K. George, Department of Urology, Walsgrave Hospital, Clifford Bridge Road, Walsgrave, Coventry CV2 2DX.

Male and Female Sexual Function and Activity Following Ileal Conduit Urinary Diversion

G. M. NORDSTRÖM and C. R. NYMAN

Department of Urology, Sodersjukhuset, Stockholm, Sweden

Summary—A group of 66 patients (40 males, 26 females) underwent an ileal conduit urinary diversion because of bladder cancer (44 patients) or incontinence/bladder dysfunction (22). They were questioned about pre- and post-operative sexual function and activity and it was found that 90% of the males (26/29) who were sexually active before surgery lost the ability to achieve erection following radical cystectomy. Although they were unable to achieve penile erection, 41% were able to experience orgasm by means of masturbation. Five of the 29 males received penile implants. Five of the 6 females treated by cystectomy, who were sexually active before the operation, reported either a decrease or cessation of sexual activity (*i.e.* coitus) post-operatively.

The main problems were a decrease in sexual desire, dyspareunia and vaginal dryness. One woman reported the inability to experience orgasm after surgery. Compared with women with bladder cancer, those with incontinence/bladder dysfunction were more likely to have an active sexual life after urostomy surgery. Seven females in this group, of whom 4 were sexually inactive before surgery, increased their sexual activity after the operation. For these women the conduit operation removed the need to use incontinence pads or indwelling catheters.

Although the creation of an ileal conduit has been the most common procedure for urinary diversion over the last 40 years (Bricker, 1950), there is little information about sexual function and activity following urostomy surgery. The high risk of sexual impotence following cystectomy was reported by Romanus (1948) and subsequent studies describe sexual impotence following radical cystectomy for bladder cancer in approximately 90% of male patients (Bergman *et al.*, 1979; Schover *et al.*, 1986). Compared with males, the sexual consequences for females following this operation seem to be less drastic. Schover and Eschenbach (1985) reported that most females resumed sexual activity, although they experienced some degree of vaginal dryness, tightness and pain. However, both physical and emotional factors, such as a decrease in sexual attractiveness, may influence sexual life following ostomy surgery (Gloeckner, 1984; Boyd *et al.*, 1987).

In the present study special attention has been paid to the extent to which gender, diagnosis and surgical procedure have influenced sexual function and activity.

Patients and Methods

Sexual function and activity were investigated in 66 patients (40 males and 26 females); 44 patients had undergone ileal conduit urinary diversion as a result of carcinoma of the bladder (Table 1). Forty patients (31 males, 9 females) had received pre-operative radiotherapy (36 Gy 4–6 weeks before the operation or 20 Gy 1 week before) and 3 patients (2 males, 1 female) had received radiotherapy at an earlier stage. In 1 woman the cystectomy was performed without previous irradiation.

Incontinence/bladder dysfunction led to urinary diversion in 22 patients (Table 2).

The age distribution at operation was 20 to 76 years (mean 55). The time that had elapsed since surgery ranged from 3 to 14 years (mean 7).

Table 1 Type of Surgery in 44 Patients with Bladder Cancer

Type of surgery	Males (n = 33)	Females (n = 11)	Total (n = 44)
Urinary diversion	33	11	44
Cystectomy	32	11	43
Prostatectomy	32	—	32
Vesiculectomy	32	—	32
Urethrectomy	30	11	41
Hysterectomy	—	2	2
Salpingectomy	—	2	2
Oophrectomy	—	0	0
Vaginal resection	—	1	1

A detailed description of the selection of patients is presented by Nordström *et al.* (1990).

An interview comprising open-ended and closed questions was used for data collection. The questionnaire was based on studies by Bergman *et al.* (1979), Jones *et al.* (1980), Studer and Furger (1981) and our own clinical experience. The questions concentrated on pre- and post-operative sexual function and activity and covered the following topics: sexual desire, erection, frequency of coitus, coital and non-coital ability to experience orgasm, causes of increased or decreased sexual activity and overall satisfaction with sexual life.

All interviews were performed by the same enterostomal therapy nurse (G.N.) either at the Stoma Care Unit, Södersjukhuset (57 patients) or in the patient's home (9 patients). Supplementary details regarding diagnosis, surgical technique and treatment were taken from the patient's medical records.

Statistical calculations were performed according to the SAS program package. Owing to the small

number of patients in some categories, Fisher's exact test was used after condensing the data into 4-fold tables. For analysis of 2 dependent groups, the McNemar test for the significance of changes was used (Siegel, 1956; Iverson Shelly, 1984). All hypotheses were tested by 2-tailed tests; $P < 0.05$ was regarded as statistically significant and $0.05 < P < 0.10$ indicated a tendency.

Results

Sexual function and activity in 33 males with bladder cancer

During the year prior to surgery, 29/33 men (88%) stated that they were able to achieve erection sufficient to perform coitus and to experience orgasm (Table 3). Four of the 33 males (12%) did not have intercourse during this period, 3 on account of old age (65, 69 and 70 years) and 1 (aged 53) because of problems related to bladder cancer. Post-operatively, 3 males (10%) were able to achieve penile erection sufficient to perform coitus. The urethra had been preserved in 2 patients and all 3 had received pre-operative radiotherapy.

Males aged 50 years or less were more likely to have preserved the ability to achieve erection after surgery (3/4) than those above that age ($P < 0.001$). Table 4 shows sexual function and activity with regard to diagnosis, gender and age.

Although unable to achieve penile erection, 12/29 men (41%) stated that they were able to experience orgasm by means of masturbation (Table 3). Nine of these achieved orgasm by masturbation alone.

Figure 1 shows the change in sexual activity (*i.e.*

Table 2 Indications for Urinary Diversion in Patients with Incontinence/Bladder Dysfunction

Diagnosis	Males	Females	Total
Neurogenic bladder due to:	5	5	10
Spinal cord injury	(4)	(1)	(5)
Congenital malformation	(1)	(2)	(3)
Diabetes mellitus	(0)	(1)	(1)
Unknown aetiology	(0)	(1)	(1)
Status after radiation therapy for gynaecological cancer	—	4	4
Chronic urethritis	0	3	3
Incontinence (not specified)	1	2	3
Status after prostatectomy	1	—	1
Chronic pyelonephritis	0	1	1
Total	7	15	22

Table 3 Sexual Function in 40 Males before and after Urinary Diversion

<i>Sexual function</i>	<i>Bladder cancer (n = 33)</i>		<i>Incontinence (n = 7)</i>	
	<i>Pre-op.</i>	<i>Post-op.</i>	<i>Pre-op.</i>	<i>Post-op.</i>
Erection (E)	29	3	3	2
Penile implant (PI)	0	5	0	0
Coitus (E + PI)	29	8	3	2
Orgasm/coitus (E)	29	2	2	1
Orgasm/coitus (PI)	0	2	0	0
Orgasm/masturbation without erection (3 PI)	—	12	—	0
Sexual activity (coitus and/or masturbation)	—	17	—	2
No coitus	4	25	4	5

Table 4 Male and Female Sexual Function and Activity with regard to Age and Diagnosis

<i>Sexual function and activity</i>	<i>No. of patients</i>	<i>Mean age at operation (years)</i>	<i>Range (years)</i>
Males (bladder cancer)	33	56.4	42–72
Pre-op. erection and coitus	29	57.2	42–72
Pre-op. inactivity	4	64.3	65–70
Post-op. erection and coitus	3	45.3	42–50
Post-op. loss of erection	26	59.0	42–72
Males (incontinence/bladder dysfunction)	7	51.3	37–71
Pre-op. erection and coitus	3	43.0	37–47
Pre-op. inactivity	4	57.5	39–71
Post-op. erection and coitus	2	41.0	37–45
Post-op. loss of erection	1	47.0	47
Females (bladder cancer)	11	57.9	43–67
Pre-op. sexual activity	6	54.2	43–62
Pre-op. sexual inactivity	5	62.4	53–69
Post-op. sexual activity	4	55.0	50–62
Post-op. loss of sexual activity (i.e. ceased coitus)	2	52.5	43–62
Females (incontinence/bladder dysfunction)	15	46.2	20–64
Pre-op. sexual activity	6	41.6	20–56
Pre-op. sexual inactivity	9	45.4	20–64
Post-op. sexual activity	9*	41.2	20–60
Post-op. loss of sexual activity (i.e. ceased coitus)	1	37.0	37

* Including 4 patients sexually active pre-operatively

coital frequency) following urostomy surgery. Among the 3 males (bladder cancer) with unchanged sexual activity, penile erection was preserved in 1, and 2 were given penile implants on account of impotence. All 3 stated that they had coitus weekly.

Of the 29 males who were sexually active before operation, 26 (90%) stated that sexual function and activity were impaired after surgery (Fig. 1). Radical cystectomy (i.e. cystectomy, prostatectomy, vesiculectomy, urethrectomy) was performed in 25 of the 26 patients. The remaining man was operated on because of urethral stricture and contracted bladder following primary irradiation for bladder

carcinoma. Twenty-one of the 26 patients discontinued intercourse because of erectile impotence. Five patients who were still able to perform coitus (3 with penile implants, 2 by erection) nevertheless experienced considerable decrease in sexual activity. Comparison of pre- and post-operative sexual status showed a statistically significant decrease in sexual function, i.e. erectile ability ($P < 0.001$), and sexual activity, i.e. coital frequency ($P < 0.001$).

Despite post-operative sexual impairment, 14/29 males (48%) who were sexually active before operation considered that their overall sexual life was satisfactory. The remaining 15 (52%) were not satisfied.

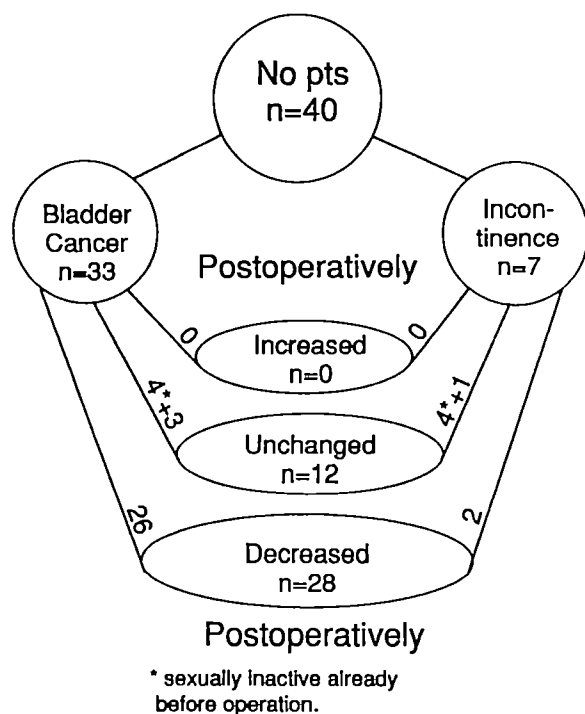


Fig. 1 Post-operative change in male sexual activity following ileal conduit urinary diversion

Sexual function and activity in 7 males with incontinence/bladder dysfunction

During the year prior to surgery, 3/7 males stated that they were sexually active and able to perform coitus (Table 3). Pre-operative sexual inactivity in

3 males was due to spinal cord injury and 1 man had earlier become impotent following prostatectomy.

Figure 1 shows the change in frequency of coitus following urostomy surgery. One man with incontinence (aged 45 at operation) resumed his former sexual life with coitus monthly. Two men reported decreased sexual activity. One of them, who was tetraplegic, did not attribute this directly to the stoma and surgery. The other ceased having intercourse because of erectile impotence of unknown aetiology. Cystectomy was not performed in any of these patients. Neither of the 2 sexually active men considered his overall sexual life to be satisfactory.

Sexual function and activity in 11 females with bladder cancer

During the year prior to surgery, 6/11 females (55%) were sexually active and they were all able to experience orgasm at intercourse (Table 5). They considered their sexual life to be satisfactory. The causes of sexual inactivity in 5 women are shown in Table 6. Compared with males (4/33), females with bladder cancer were more likely to be sexually inactive (5/11) before the operation ($P < 0.05$).

Figure 2 shows the post-operative change in the frequency of coitus. One woman remained sexually active after pre-operative irradiation and surgery and continued to have intercourse weekly; she was aged 52 at operation.

Table 5 Sexual Function in Females before and after Urinary Diversion

Sexual function	Bladder cancer (n=11)		Incontinence (n=15)	
	Pre-op.	Post-op.	Pre-op.	Post-op.
Coitus	6	4	6	9
Orgasm/coitus	6	3	4	6
Orgasm/masturbation	—	2	—	5
Sexual activity (coitus and/or masturbation)	—	5	—	10
No coitus	5	7	9	6

Table 6 Causes of Pre-operative Sexual Inactivity in Females

Causes	Bladder cancer	Incontinence	Mean (years)	Age range (years)
Lack of interest	2	4	62	53–69
Disabling incontinence	0	5	40	20–60
Absence of partner	2	0	60	53–67
Disease-related problems	1	0	59	59
Total	5	9	55	20–69

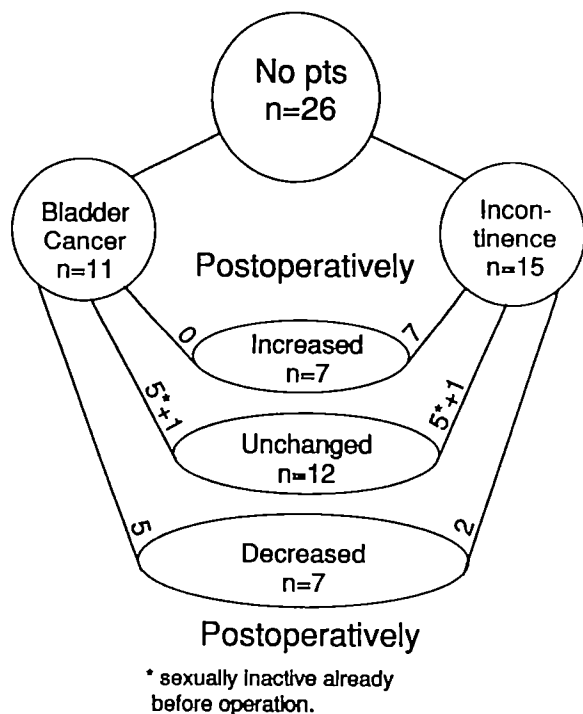


Fig. 2 Post-operative change in female sexual activity following ileal conduit urinary diversion.

In the remaining 5 females with bladder cancer, sexual activity and function were impaired after the operation (Fig. 2). Pre-operative radiotherapy followed by radical cystectomy were performed in all of these patients. Three females reported decreased sexual activity and 2 ceased having intercourse. Compared with the pre-operative sexual status, there was a tendency ($P=0.06$) towards decreased sexual activity in these women. Problems such as decrease in sexual desire (5 patients), dyspareunia (3), vaginal dryness (2) and anorgasm (1) were reported. Despite decreased sexual activity in the majority of females, only 1 considered her overall sexual life to be unsatisfactory.

Sexual function and activity in 15 females with incontinence/bladder dysfunction

Nine of the 15 females in this group (60%) were sexually inactive prior to the operation because of incontinence and lack of interest (Table 6).

Six females (40%) were sexually active within 1 year of surgery (Table 5). Despite this, 3 of them considered their sexual life to be unsatisfactory owing to disabling incontinence. Four patients stated that they were able to experience orgasm and

the remaining 2, who suffered from neurogenic disorders, were unable to do so. Unlike the bladder cancer group, there was no significant difference between males and females with regard to pre-operative sexual activity.

Figure 2 shows the post-operative change in frequency of coitus. One woman (aged 48 at operation) continued to have intercourse weekly and also experienced orgasm.

Decreased sexual activity was reported by 2 females (Fig. 2). One stated that changes in her perceived body image were responsible and 1 ceased having intercourse because of dyspareunia but was able to experience orgasm by non-coital stimulation. Both considered their overall sexual life to be unsatisfactory.

Seven females (47%), of whom 4 were sexually inactive before surgery, reported both increased sexual activity (Fig. 2) and increased sexual desire after the operation (mean age at operation 38 years; range 20–60) and found their overall sexual life to be more satisfying. The conduit operation removed the need to use incontinence pads or indwelling catheters. Comparison of pre- and post-operative sexual activity in this group revealed no statistically significant difference. However, comparison of females with bladder cancer with those suffering from incontinence/bladder dysfunction showed the latter group to be more likely to increase sexual activity after surgery ($P<0.05$).

Discussion

The present study has adopted a biological and physiological approach to sexual function and activity before and after ileal conduit urinary diversion.

As in other studies (Bergman *et al.*, 1979; Schover *et al.*, 1986a), erectile impotence after cystectomy for bladder cancer was reported in approximately 90% of males. Injury to the pelvic autonomic plexus during dissection around the prostate and urethra (Lue *et al.*, 1984; Lepor *et al.*, 1985), as well as damage to the pelvic vascular system (Bergman *et al.*, 1982), are reported to contribute to loss of erectile function. However, by using a "nerve-sparing" technique, Walsh and Mostwin (1984) succeeded in preserving erectile function after radical cystoprostatectomy in 9/11 males.

Studies on the recovery of sexual function after cystectomy have implied that males who had intercourse more frequently before surgery maintained a higher level of post-operative sexual

activity, were generally younger (mean 59 years) and had younger wives (Schover *et al.*, 1986). Our 3 men with preserved erectile ability were all aged 50 years or less at the time of surgery, were all married, had sexual intercourse at least once a week pre-operatively and considered sexuality important. Bergman *et al.* (1982) confirmed that younger men were more likely to regain functional erections.

Kinsey *et al.* (1948) reported that orgasm could occur without ejaculation and flow in the urethra, *i.e.* dry orgasm. Bergman *et al.* (1982) used electromyographic recordings to show contractions of the bulbocavernosus and levator ani muscles without emission of semen. Dry orgasm was experienced by half of our males with bladder cancer and is in accord with previous reports (Bergman *et al.*, 1979; Schover *et al.*, 1986).

Amongst our males with bladder cancer, 5/29 (17%) were given penile implants. Almost the same proportion (13/73; 18%) was reported by Schover *et al.* (1986), while the corresponding figure given by Boyd *et al.* (1987) was 30%. Amongst our male patients with penile implants, 3/5 reported decreased sexual activity. The psychosocial outcome of penile implants has been studied by Mindus *et al.* (1983), who found that 69% of their patients were satisfied.

The group of males with incontinence/bladder dysfunction was very heterogeneous with regard to age and underlying disease (Table 2) and each disease affects sexual function in its own specific way. This, together with the limited number of patients in each subgroup, made it impossible to draw valid conclusions.

Schover and Eschenbach (1985) studied pre- and post-operative sexual function and activity in 9 females sexually active before cystectomy. Although the initial problem was mainly dyspareunia owing to vaginal dryness and tightness, the majority (7/9) resumed a satisfying sex life.

From the female point of view, intact anatomy, vaginal blood flow, nerve supply and hormonal support mechanisms are prerequisites for optimal sexual function (Kolodny, 1979; Levin, 1980, 1981). In both females and males who undergo cystectomy, the pudendal nerve remains intact, which indicates preserved clitoral and vaginal sensitivity, but one would expect loss of vaginal blood flow and lubrication as a result of damage to the peripheral, autonomic nerve fibres (Schover and Eschenbach, 1985; Schover, 1986). Our study group, like that of Schover and Eschenbach (1985), was small and based on the females' subjective data. Objective investigations of vaginal blood flow and pelvic

contractions before and after cystectomy are needed to verify the subjective results.

Females undergoing surgery because of incontinence/bladder dysfunction were more likely to lead an active sexual life after urostomy surgery (7/9) than those with bladder cancer. Four of these patients were not sexually active before surgery because of disabling incontinence that was inadequately controlled by an appliance. These results confirm those reported by Desmond and Shuttleworth (1977). Moreover, females treated for disabling incontinence by urinary diversion experienced an improvement in their quality of life and sociability (Malone *et al.*, 1985).

Our study group was heterogeneous with regard to gender, age, diagnosis and surgical procedure. The common denominator was the need to adjust to an external stoma and appliance. Whether sexual dysfunction is basically biogenic/organic or psychogenic in nature is a matter of debate. Several factors may affect sexuality (Derogatis and Kourlesis, 1981). They include (1) the disease process itself (bladder cancer or incontinence/bladder dysfunction); (2) the surgical procedures and other treatment (*e.g.* radiotherapy, chemotherapy); (3) psychological disorders (anxiety, depression); (4) body image alterations due to an external stoma and appliance and/or physical disability following trauma or congenital disorders; (5) the reaction of others to illness and disability; (6) the patients' general health and the aging process itself. All of these factors must be considered when evaluating an individual's sexual function and activity. It may be concluded that sexual dysfunction in males following radical cystectomy for bladder cancer seems to be mainly biogenic/organic in origin. The radical nature of the surgery and the patient's age may also play a role. Female sexual function and activity following this operation are more difficult to evaluate, although biogenic/organic and psychogenic factors are also likely to be involved. Males and females with incontinence/bladder dysfunction form a heterogeneous group, especially with regard to the underlying disease, and biogenic/organic and psychogenic factors influence their sexual function and activity.

Acknowledgements

This study was supported by grants from the Swedish Delegation for Social Research (No. 82/93:2), the Stockholm College of Health and Caring Sciences, The Swedish Cancer Society (No. 89:421), the Karolinska Institute, the ConvaTec Scholarship Fund and the Opuscula Medica Association. We are grateful to Mr B. Ramund, statistician at the Department of Education, University of Uppsala, for his help and advice.

References

- Bergman, B., Nilsson, S. and Petersen, I. (1979). The effect on erection and orgasm of cystectomy, prostatectomy and vesiculectomy for cancer of the bladder: a clinical and electromyographic study. *Br. J. Urol.*, **51**, 114–120.
- Bergman, B., Silvertsson, R. and Saarikula, M. (1982). Penile blood pressure in erectile impotence following cystectomy. *Scand. J. Urol. Nephrol.*, **16**, 81–84.
- Boyd, S. D., Feinberg, S. M., Skinner, D. G. *et al.* (1987). Quality of life survey of urinary diversion patients: comparison of ileal conduits versus continent Kock ileal reservoirs. *J. Urol.*, **138**, 1386–1389.
- Bricker, E. M. (1950). Bladder substitution after pelvic evisceration. *Surg. Clin. North Am.*, **30**, 1511–1521.
- Derogatis, L. R. and Kourlesis, S. M. (1981). An approach to evaluation of sexual problems in the cancer patient. *CA*, **31**, 46–50.
- Desmond, A. D. and Shuttleworth, K. E. D. (1977). The results of urinary diversion in multiple sclerosis. *Br. J. Urol.*, **49**, 495–502.
- Gloeckner, M. R. (1984). Perceptions of sexual attractiveness following ostomy surgery. *Res. Nurs. Health*, **7**, 87–92.
- Iverson Shelly, S. (1984). *Research Methods in Nursing and Health*. Chapter 18–19, pp. 495–589. Boston, Toronto: Little, Brown.
- Jones, M. A., Breckman, B. and Hendry, W. F. (1980). Life with an ileal conduit: results of questionnaire surveys of patients and urological surgeons. *Br. J. Urol.*, **52**, 21–25.
- Kinsey, A. C., Pomeroy, W. B., Martin, C. E. *et al.* (1948). *Sexual Behaviour of the Human Male*. Philadelphia: Saunders.
- Kolodny, R. C. (1979). *Textbook of Human Sexuality for Nurses*. Boston, Toronto: Little, Brown.
- Lepor, H., Gregerman, M., Crosby, R. *et al.* (1985). Precise localization of the autonomic nerves from the pelvic plexus to the corpora cavernosa: a detailed anatomical study of the adult male pelvis. *J. Urol.*, **133**, 207–212.
- Levin, R. J. (1980). The physiology of sexual function in women. *Clin. Obstet. Gynecol.*, **7**, 213–252.
- Levin, R. J. (1981). The female orgasm—a current appraisal. *J. Psychosom. Res.*, **25**, 119–133.
- Lue, T. F., Zelen, S. J., Schmidt, A. *et al.* (1984). Neuroanatomy of penile erection: its relevance to iatrogenic impotence. *J. Urol.*, **131**, 273–280.
- Malone, P. R., Stanton, S. L. and Riddle, P. R. (1985). Urinary diversion for incontinence—a beneficial procedure. *Ann. R. Coll. Surg. Engl.*, **67**, 349–352.
- Mindus, P., Berg, R., Berg, G. *et al.* (1983). Viktigt att bedöma risk för psykosocialt misslyckande innan implantat görs vid erektil impotens. *Läkartidningen*, **80**, 245–247.
- Nordström, G., Borglund, E. and Nyman, C. R. (1990). Local status of the urinary stoma—the relation to peristomal skin complications. *Scand. J. Urol. Nephrol.*, **24**, 117–120.
- Romanus, R. (1984). Cystectomy in the male, the significance of the combined prostatico-urethral vesiculo-cystectomy with special reference to the sexual function. *Acta Chir. Scand.*, **97**, 389–409.
- Schover, L. R. (1986). Sexual rehabilitation of the ostomy patient. In *Ostomy Care and the Cancer Patient*, ed. Smith, D. B. and Johnson, D. E. First edition. Chapter 7, pp. 103–119. Orlando: Grune and Stratton.
- Schover, L. R., Evans, R. and von Eschenbach, A. C. (1986). Sexual rehabilitation and male radical cystectomy. *J. Urol.*, **136**, 1015–1017.
- Schover, L. R. and von Eschenbach, A. C. (1985). Sexual function and female radical cystectomy: a case series. *J. Urol.*, **134**, 465–468.
- Siegel, S. (1956). *Nonparametric Statistics for the Behavioural Sciences*. New York: McGraw Hill.
- Studer, U. and Furger, P. (1981). Die psycho-soziale Reintegration des Urostomapatienten. *Schweiz. Med. Wochenschr.*, **111**, 1834–1839.
- Walsh, P. C. and Mostwin, J. L. (1984). Radical prostatectomy and cystoprostatectomy with preservation of potency. Results using a new nerve-sparing technique. *Br. J. Urol.*, **56**, 694–697.

The Authors

G. M. Nordström, DrMedSci, RNT, ET.
C. R. Nyman, MD, Assistant Professor.

Requests for reprints to: G. M. Nordström, Wadköpingsvägen 24, 161 51 Bromma, Sweden.

Cystoprostatectomy and Substitution Cystoplasty for Locally Invasive Bladder Cancer

P. J. THOMAS, DIANE E. NURSE, C. DELIVELIOTIS and A. R. MUNDY

Department of Urology, Guy's Hospital, London

Summary—The results and long-term follow-up of 48 patients undergoing cystoprostatectomy and substitution cystoplasty for T2/3, M0 transitional cell carcinoma of the bladder are reported. There was no operative mortality but 1 early death from thromboembolic disease. Thirty-six patients are alive with a mean follow-up of 57 months (range 12–120). Eleven patients died of disseminated disease. Thirty-one patients (64%) regained normal continence by day and night and a further 8 were dry by day but incontinent at night; 9 patients underwent further surgery for incontinence and this was successful in 8, giving an overall continence rate of 79% and a day-time continence rate of 98%. Of the 38 patients claiming to be potent pre-operatively, 24 (63%) were potent post-operatively. Nerve-sparing cystoprostatectomy and substitution cystoplasty is a safe alternative to a "standard" cystectomy and ileal conduit diversion in a selected group of men undergoing radical surgery for invasive bladder cancer and it achieves its aims of preserving continence and potency in the majority of patients.

There is still considerable debate in the UK as to whether radical surgery or radical radiotherapy should be the first line of treatment for locally invasive transitional cell carcinoma of the bladder. At least part of this debate concerns the mortality and morbidity associated with surgery and particularly the incidence of impotence and the historical need for urinary diversion related to cystectomy.

Five years ago we reported our early experience with a small number of patients treated by cystoprostatectomy and substitution cystoplasty (Mundy *et al.*, 1986). This report describes our more recent experience with longer-term follow-up.

Patients and Methods

The study group comprised 48 male patients with a mean age of 61 years (range 39–72) who were selected for cystoprostatectomy and substitution cystoplasty. All had a T2 or T3, M0 transitional cell carcinoma. Investigations included examination

under anaesthesia and chest X-ray. In all instances there was a solitary tumour with no evidence of nodal or distant metastasis on CT scanning and no evidence of disease at or below the level of the bladder neck on routine random biopsy. Patients with multifocal disease or with urothelial abnormalities at or below the bladder neck on random biopsy were excluded (but see below).

In all instances patients were selected only if they were adequately motivated to "relearn" continence and all patients were offered an ileal conduit urinary diversion as an alternative.

Eleven patients had staged radiotherapy followed by surgery; 16 patients had salvage surgery after failed radiotherapy and 21 patients had surgery alone.

All patients said that they were continent and 38 claimed to be potent pre-operatively. It was not thought justifiable to prove either assertion by objective means.

The surgical technique, using an unmodified right colonic segment for the substitution cystoplasty, was as described by Mundy *et al.* (1986) except that in patients who had previously had a radical course of radiotherapy the cystoplasty segment of right colon was patched with adjacent

ileum to detubularise it. The anterior taenia coli of the segment of right colon was opened along its length through the ileocaecal valve and along the antimesenteric border of the ileum. The ileum was then sewn into opened colon to form a pouch. This was because our previous experience had shown that after radiotherapy there was a high incidence of sphincter weakness and these patients therefore had a troublesome incidence of symptoms from contractility of the cystoplasty segment.

Results

Complications

The complications are listed in the Table. Although there was no operative mortality, 1 patient died the day after discharge from hospital from a massive pulmonary embolus. Complications were seen in 7/27 patients (26%) subjected to previous radiotherapy but in only 1/21 (5%) treated by surgery alone. No patient developed symptoms or required treatment for a metabolic disorder attributable to the cystoplasty.

Survival and local recurrence

The mean follow-up was 57 months (range 12–120). Eleven patients died from recurrent disease, in all cases from metastasis. Only 1 patient had a recurrence at the cystoplasty-urethral anastomosis and this caused incontinence, not obstruction, and was therefore not a direct cause of death; 36 patients are alive and disease-free.

Continence

Continence was assessed subjectively and objectively by videourodynamic studies 6 months post-operatively. At this time 31 patients (64%) claimed to be continent by day and night; 8 patients (17%) said they were continent by day but occasionally or regularly incontinent at night; 9 patients (19%) were incontinent by day and night.

Videourodynamic studies showed that 5 of the 9 patients incontinent by day and night had sphincter weakness; 3 of these were subsequently shown to have a sphincter stricture (all had had radiother-

apy). Four patients had an over-active unmodified cystoplasty segment. All 9 underwent revisional surgery; 5 received an artificial urinary sphincter (AUS) and in 4 cases this was successful; 1 patient developed a cuff erosion and remained incontinent until his death (he too had had radiotherapy). Three had their cystoplasty "patched" with ileum to detubularise it and 1 had both a patch and an AUS. The procedure was successful in these 4 cases. In the 8 patients wet by night and dry by day no identifiable cause could be found and they used a condom drainage device; 5 patients who claimed to be continent by day and night showed objective evidence of sphincter weakness.

In no case was there subjective deterioration of continence post-operatively, except for the one patient who died with a local recurrence and who became wet shortly before death.

Impotence

Eight patients (30%) who had radiotherapy were impotent pre-operatively compared with 2 (5%) of those who had not. Of the 38 patients who claimed to be potent pre-operatively, 24 (63%) remained potent by their own assessment post-operatively. The incidence of post-operative impotence was similar in both groups, 8 (42%) of those who had previous radiotherapy and 6 (31%) of those undergoing surgery alone becoming impotent.

Discussion

Continence and potency can be retained after radical surgery for bladder cancer as Walsh has shown for prostate cancer (Quinlan *et al.*, 1991; Steiner *et al.*, 1991). Preservation of both neurovascular bundles gives the best chance of retaining potency but we have found that the patient will be impotent if even one bundle has been damaged. Irrespective of whether a cystoplasty is performed, a potency-preserving cystectomy is desirable and achievable in the majority of cases.

Previous radiotherapy undoubtedly increases peri-operative morbidity and mortality, and also long-term morbidity; it slows healing of the cystoplasty-urethral anastomosis and significantly re-

Table Peri-operative Complications in 48 Patients

Complication	Surgery alone (n = 21)	Radiotherapy (n = 27)
Thromboembolic	1	3
Delayed healing of anastomosis	—	2
Intestinal obstruction	—	2
Total	1 (5%)	7 (26%)

duces the likelihood of achieving continence. Radiotherapy, however, has little effect on post-operative potency, although fewer patients will be potent initially. These findings suggest that for both potency and continence the damage is done as much (or more) by the radiotherapy as by the surgery. Problems with potency can be anticipated from the pre-operative status but problems with continence cannot be anticipated as long as the bladder neck sphincter mechanism remains intact.

One-third of patients had post-operative incontinence but half of these were wet only at night and were satisfactorily managed with a condom drainage device. None of them had an abnormality on the videourodynamic study and the mechanisms responsible are being investigated further. An overactive cystoplasty segment was responsible for incontinence in 5 patients, necessitating further surgery. This raises the question of the role and value of "detubularisation" of the cystoplasty. The results presented here show that 12% of patients undergoing a "straight" cystoplasty will require a detubularisation procedure subsequently to deal with troublesome colonic contractions. It might therefore appear reasonable to detubularise the cystoplasty routinely, despite the fact that in the vast majority it would be unnecessary. The problem is that many patients who have a detubularised cystoplasty either do not void very efficiently or need to self-catheterise. Our experience of male patients on long-term intermittent self-catheterisation is that 50% have developed urethral strictures by 2 years of follow-up. This seems a high potential complication rate in the 88% who would not have troublesome colonic contractions in any case.

Although excluded from this study, men with multifocal disease and women with bladder cancer present a further challenge because in both instances a total cystourethrectomy is usually required. The question then arises, if the patient is to be reconstructed, of how to fashion a continence mechanism. We have found the most reliable way is to fashion a neo-urethra from colon in continuity with a colonic substitution cystoplasty (Mundy, 1992). The colonic neo-urethra is tunnelled in to a taenia coli to provide a flap valve type of continence mechanism. This has the advantage that the procedure can be used either for continent diversion, if the neo-urethral meatus is brought out on the abdominal wall (preferably at the umbilicus where it will be concealed), or alternatively rotated down to the perineum for lower urinary tract reconstruction in females.

Although no patient needed treatment for meta-

bolic complications of the neobladder, previous studies (Nurse and Mundy, 1989a) have shown that all will have a metabolic acidosis and may be at risk of potential malignant complications (Nurse and Mundy, 1989b). In adult patterns with malignant disease, these are theoretical rather than practical problems because of their limited life expectancy, but nonetheless warrant further investigation.

Finally, although some patients take some time to regain continence after a substitution cystoplasty and may require additional surgical procedures, only 13% ultimately used a condom drainage device, all but one only at night. Following an ileal conduit urinary diversion, adaption to the abdominal wall appliance in both psychological and practical terms can be slow and some patients will suffer complications from the stoma which may need surgical revision (Jones *et al.*, 1980). In our experience, many male patients prefer to be incontinent through the natural orifice into a condom type drainage device with a bag attached to the inside of their leg than through a stoma on their abdominal wall. Thus, even if cystoprostatectomy and substitution cystoplasty were followed by both impotence and incontinence, many men would still regard themselves as being better off than if they had had a standard cystectomy and ileal conduit.

References

- Jones, M. A., Breckman, B. and Hendry, W. F. (1980). Life with an ileal conduit: results of questionnaire surveys of patients and urological surgeons. *Br. J. Urol.*, **52**, 21-25.
- Mundy, A. R. (1992). Total substitution of the lower urinary tract. A technique for either reconstruction or continent diversion. *Br. J. Urol.* (In press).
- Mundy, A. R., Nurse, D. E., Dick, J. A. *et al.* (1986). Continence and potency-preserving cystoprostatectomy and substitution cystoplasty for patients with bladder cancer. *Br. J. Urol.*, **58**, 664-668.
- Nurse, D. E. and Mundy, A. R. (1989a). Metabolic complications of cystoplasty. *Br. J. Urol.*, **63**, 165-170.
- Nurse, D. E. and Mundy, A. R. (1989b). Assessment of malignant potential of cystoplasty. *Br. J. Urol.*, **64**, 489-492.
- Quinlan, D. M., Epstein, J. I., Carter, B. S. *et al.* (1991). Sexual function following radical prostatectomy: influence of preservation of neurovascular bundles. *J. Urol.*, **145**, 998-1003.
- Steiner, M. S., Morton, R. A. and Walsh, P. C. (1991). Impact of anatomical radical prostatectomy on urinary incontinence. *J. Urol.*, **145**, 512-514.

The Authors

P. J. Thomas, FRCS, Senior Registrar
 Diane E. Nurse, FRCS(Urol.), Senior Registrar.
 C. Deliveliotis, MD, Lecturer
 A. R. Mundy, MS, FRCS, MRCP, Professor of Urology.

Requests for reprints to: A. R. Mundy, Department of Urology, Guy's Hospital, St Thomas' Street, London SE1 9RT.

Survey of Urological Centres and Review of Current Practice in the Pre-operative Assessment of Prostatism

A. G. WILKINSON and S. R. WILD

Department of Radiology, Western General Hospital, Edinburgh

Summary—A survey of 24 urological centres has shown a wide variation in the routine pre-operative assessment of patients being considered for prostatectomy. Imaging of the urinary tract by intravenous urography (IVU) or ultrasound (US) is performed in 21/24 centres (79%) and plain films in 16/24 (67%). Post-micturition residual volume (PMRV) is estimated quantitatively in 10/24 centres (42%). Although there is little agreement on what constitutes a significant PMRV, a large PMRV leads to increased likelihood of operation, and earlier operation. Peak urine flow rate (Q max) is measured in 19/24 centres (79%). The significance of these findings is discussed.

The pre-operative assessment of patients presenting with symptoms of uncomplicated benign prostatic hypertrophy has been the subject of several studies (Fidas *et al.*, 1987; de Lacey *et al.*, 1988; Jensen *et al.*, 1988a, b; Timoney *et al.*, 1989) but there is little consensus as to which, if any, imaging investigations should be performed. We conducted a survey of 24 urological centres in Britain to determine current practice in the pre-operative assessment of patients being considered for prostatectomy.

Materials and Methods

Questionnaires were sent to 24 consultant urological surgeons regarding their routine investigation of patients presenting with symptoms of uncomplicated benign prostatic hypertrophy; 13 surgeons worked in teaching hospitals and 9 in district general hospitals.

Results

We received 24 replies. Answers to the question "Which of the following are routinely performed in your department prior to transurethral resection of the prostate (TURP) in patients thought clinically

Table 1 Routine Pre-operative Imaging in 24 Centres

	No. of centres	(%)
IVU	7	(29)
US with estimation of PMRV	12	(50)
US without estimation of PMRV	2	(8)
Plain films	16	(67)
Q max	19	(79)
Videourodynamics	4	(17)
Other	0	(0)

to have significant prostatic hypertrophy?" are shown in Table 1.

Ten surgeons routinely estimated PMRV pre-operatively, sometimes by more than 1 method. Methods employed were: ultrasound (9 centres), IVU (2), catheterisation (1) and nuclear medicine (1).

Fourteen surgeons did not routinely estimate PMRV pre-operatively, although 2 of them examined post-micturition plain films of the abdomen and pelvis to detect a large bladder outline.

Answers to the question "How large a residual volume do you consider to be significant?" are shown in Table 2. Ten surgeons did not specify a volume that they considered to be significant.

Answers to the question "How does the knowl-

Table 2 Residual Volumes Considered to be Significant

<i>Residual volume (ml)</i>	<i>No of surgeons</i>
50	2
100	5
150	2
200	2
250	1
300	2
Total	14

Table 3 Effect on Management of a Significant Residual Volume

<i>Effect on management</i>	<i>No of surgeons</i>
Further pre-operative investigations	3
More likely to undergo operation	14
Earlier operation	7
Different operative technique	1
Different follow-up	1
Management not altered	7

edge of a significant residual volume affect the patient management?" are shown in Table 3.

Discussion

The survey supports our premise that there is widely differing practice in the pre-operative investigation of patients thought to have benign prostatic hypertrophy. IVU has traditionally been performed in these patients and Marshall *et al.* (1975) stated that in the routine out-patient there was little room for argument as to the wisdom of this investigation. The same authors, however, went on to show that abnormalities demonstrated on IVU altered clinical management in only 1 of 203 men with prostatism admitted to hospital in acute retention (a patient with a bladder diverticulum large enough to warrant operation) and concluded that the information obtained by routine urography did not justify the delay in operation and subsequent prolongation of hospital stay by more than 3 days. Although hydronephrosis was present in 38 patients, this did not alter either the decision to operate or the type of operation.

Abrams *et al.* (1976) showed that only 5% of patients with uncomplicated prostatism had upper tract dilatation on IVU and that this was not significantly associated with outflow obstruction; 7% of patients had coexisting upper tract pathology

but none had renal cancers or other abnormality that altered management.

Fidas *et al.* (1987) showed that ultrasound was as sensitive as IVU in the detection of renal tract abnormalities and suggested that routine urography in patients presenting with prostatism should be abandoned. De Lacey *et al.* (1988) went further and suggested that there was little or no benefit from routine pre-operative IVU or US examination of the urinary tract. Brooks (1988) confirmed the very low rate of detection of asymptomatic renal cancers in patients with uncomplicated prostatism—only 0.16% of 3128 patients undergoing routine urography without nephrotomography.

In spite of this evidence, our survey revealed that IVU is still performed routinely in 29% of centres, and that imaging by IVU or US is performed in 21 of 24 centres. Plain films of the abdomen and pelvis are performed in 67% of centres but since renal stones rarely alter clinical management (Marshall *et al.*, 1975; Wilkinson and Wild, 1992) and bladder stones will be found at cystoscopy, there seems little justification for this.

It was found that 42% of surgeons routinely estimated PMRV pre-operatively, mainly by ultrasound. Three surgeons added the comment that a single estimation of PMRV should be treated with caution because of poor reproducibility. Bruskewitz *et al.* (1982) showed considerable variation in PMRV in the same patient on different occasions and failed to show a correlation between PMRV and symptomatology or cystoscopic or urodynamic findings. Anderson (1982) found a relation between PMRV and urodynamic parameters reflecting the function of the detrusor muscle but not Q max. Wilkinson and Wild (1992) showed a statistically significant negative correlation between PMRV and Q max. Of the 14 surgeons who did not estimate PMRV routinely, 2 examined post-micturition plain films for a large bladder outline. The reliable demonstration of a large PMRV on plain films was documented by Morewood and Scally (1986) and Wilkinson and Wild (unpublished data) have confirmed this finding. Timoney *et al.* (1989) claimed to show a relation between PMRV and the size of the bladder outline on plain films, but the study compared plain films 1 h after micturition on the pre-operative day with residue at operation 1 h after micturition; there are several potential sources of error with this suspect methodology.

Since there is failure to agree on what constitutes a significant PMRV, with estimations varying from 50 to 300 ml, it is surprising that 7/24 surgeons commented that a significant PMRV would alter

management by leading to earlier operation. Although it has been claimed that a large PMRV is associated with the development of acute retention (Powell *et al.*, 1980), Wilkinson and Wild (1992) found that none of 59 patients developed acute retention whilst on the waiting list for prostatectomy. Even more surprising is the finding that 14/24 surgeons would be more likely to operate on patients with a large PMRV, since urodynamic data failed to support an association between PMRV and post-operative outcome (Jensen *et al.*, 1988b).

The most commonly performed investigation was peak urinary flow rate (Q max), which is carried out in 79% of centres. Jensen *et al.* (1988a) showed that a pre-operative Q max of more than 15 ml/s was associated with a poor subjective evaluation of the outcome of surgery. McLoughlin *et al.* (1990) demonstrated that 95% of men with a flow rate of 12 ml/s or less had urodynamic evidence of obstruction. Neal *et al.* (1989) claimed that pre-operative Q max did not predict the operative outcome but considered only patients with flow rates of 15 ml/s or less.

In conclusion, this survey has shown the wide variation of current pre-operative investigations in patients presenting with prostatism. Despite evidence showing low detection rates for clinically significant incidental urinary tract pathology, routine imaging is often performed. Similarly, PMRV is often estimated without evidence of benefit. Q max is commonly performed and appears to be the most useful screening test for outflow obstruction. We have also reviewed pre-operative investigations in 175 patients in this institution and evaluated their usefulness (Wilkinson and Wild, 1992).

References

- Abrams, P. H., Roylance, J. and Feneley, R. C. L. (1976). Excretion urography in the investigation of prostatism. *Br. J. Urol.*, **48**, 681–684.
- Anderson, J. T. (1982). Prostatism. III. Detrusor hyperreflexia and residual urine. Clinical and urodynamic aspects and the influence of surgery on the prostate. *Scand. J. Urol. Nephrol.*, **16**, 25–30.
- Brooks, A. P. (1988). Prostatism, intravenous urography and asymptomatic renal cancer. *Br. J. Urol.*, **62**, 1–3.
- Bruskewitz, R. C., Iverson, P. and Madsen, P. O. (1982). Value of post void residual urine determination in evaluation of prostatism. *Urology*, **20**, 602–604.
- De Lacey, G., Johnson, S. and Mee, D. (1988). Prostatism: how useful is imaging of the urinary tract? *Br. Med. J.*, **296**, 965–967.
- Fidas, A., Mackinlay, J. Y., Wild, S. R. *et al.* (1987). Ultrasound as an alternative to intravenous urography in prostatism. *Clin. Radiol.*, **38**, 479–482.
- Jensen, K. M., Jorgensen, J. B. and Morgensen, P. (1988a). Urodynamics in prostatism. I. Prognostic value of uroflowmetry. *Scand. J. Urol. Nephrol.*, **22**, 109–117.
- Jensen, K. M., Jorgensen, J. B. and Morgensen, P. (1988b). Urodynamics in prostatism. III. Prognostic value of medium fill water cystometry. *Scand. J. Urol. Nephrol. (Suppl.)*, **114**, 78–83.
- McLoughlin, J., Gill, K., Abel, P. D. *et al.* (1990). Symptoms versus flow rates versus urodynamics in the selection of patients for prostatectomy. *Br. J. Urol.*, **66**, 303–305.
- Marshall, V., Singh, M. and Blandy, J. P. (1975). Is urography necessary for patients with acute retention of urine before prostatectomy? *Br. J. Urol.*, **47**, 73–77.
- Morewood, D. J. W. and Scally, J. K. (1986). An evaluation of the post-micturition radiograph following intravenous urography. *Clin. Radiol.*, **37**, 499–500.
- Neal, D. E., Ramsden, P. D., Sharples, L. *et al.* (1989). Outcome of elective prostatectomy. *Br. Med. J.*, **299**, 762–767.
- Powell, P. H., Smith, P. J. B. and Feneley, R. C. L. (1980). The identification of patients at risk from acute retention. *Br. J. Urol.*, **52**, 520–522.
- Timoney, A. G., Payne, S. R., Davies, L. A. L. *et al.* (1989). The plain film bladder shadow in outflow obstruction: as accurate a discriminant of residual urine as ultrasound. *Br. J. Urol.*, **63**, 363–366.
- Wilkinson, A. G. and Wild, S. R. (1992). Is pre-operative imaging of the urinary tract worthwhile in the assessment of prostatism? *Br. J. Urol.*, **70**, 53–57.

The Authors

A. G. Wilkinson, MA, MRCP, FRCR, Senior Registrar.
S. R. Wild, FRCR, FRCPE, Consultant Radiologist.

Requests for reprints to: A. G. Wilkinson, Department of Radiology, Western General Hospital, Crewe Road, Edinburgh EH4 2XU.

Bladder Cancer Mortality in the Netherlands, 1955–1988

L. A. L. M. KIEMENEY, A. L. M. VERBEEK, P. J. NELEMANS, J. A. WITJES and H. STRAATMAN

Department of Epidemiology, University of Nijmegen, Nijmegen, the Netherlands

Summary—In 1955, 234 men and 116 women died from bladder cancer in the Netherlands. In 1988 the numbers were 794 and 317 respectively. After adjusting for the ageing of the Dutch population since 1955, female mortality rates per 10^5 person-years appear to be very stable: 2.9 from 1955 to 1959 and 3.0 from 1985 to 1988. By contrast, an increasing trend exists in males. From 1955 to 1959 and from 1985 to 1988, bladder cancer mortality rates per 10^5 person-years were 7.5 and 12.4 respectively. For men in particular, increasing mortality (and incidence) rates are seen all over the world. In many cases this increasing trend is thought to originate from a higher risk of dying from bladder cancer in successive birth cohorts rather than from a higher risk in successive calendar periods. This so-called cohort effect is explained by changes in smoking behaviour in the male population.

Statistical modelling of bladder cancer mortality data from 1955 to 1988 in the Netherlands shows that the increasing temporal trend in men can also be described as a cohort effect. The risk of dying from bladder cancer increases from the 1875 birth cohort to the 1910 birth cohort, but decreases thereafter. It is concluded that this decreasing risk for generations born after 1910 will probably result in a decreasing trend in mortality in the near future, when more and more of these "youngsters" reach the age of 70+.

An increase in the incidence and mortality rates of bladder cancer is seen in nearly all Western communities (Staszewski, 1980). In Alberta, Canada, male age-standardised incidence rates per 10^5 person-years increased from 10.8 in 1964 to 20.3 in 1984 (Berkel *et al.*, 1990). National cancer survey data from the USA showed a 51% increase in age-standardised rates among white men from 14.1 to 21.3 cases per 10^5 person-years in 1937 to 1939 and 1969 to 1971 respectively. In the same period the rates in Connecticut rose from 10.6 to 23.4 (Morrison and Cole, 1982). In Denmark, the age-standardised incidence rates for men increased from 10.8 in 1953 to 1957 to 24.7 in 1978 to 1982 (Doll *et al.*, 1966; Muir *et al.*, 1987). Trends in bladder cancer incidence among women are less consistent. Although a number of registries showed increasing rates, in the US national cancer survey data for example, decreasing rates were found for women.

This presentation of rates from different calendar periods is more or less the standard method of describing temporal trends in the occurrence of cancer. It is possible, however, that period of birth, instead of period of mortality, gives a better description of the observed rates. The relevance of differentiating these 2 types of temporal trend is that they may lead to very different hypothesised underlying causal factors (Day and Charnay, 1982).

Using data from the Connecticut cancer registry, Roush *et al.* (1987) demonstrated that the increase in (invasive) bladder cancer rates could be accounted for by a simple so-called age-cohort pattern in both sexes. This means that starting with some specific birth cohort the incidence is increasing for successive birth cohorts (with a similar age profile) rather than for successive calendar periods. In the Connecticut analyses, males show a consistent rise beginning at least with those born in 1870 and a peak in those born around 1930, whereas for females a sharp rise begins around 1900 with the increase persisting into at least the 1940 cohort.

According to the authors, these findings are consistent with trends by birth cohort for cigarette smoking, which strengthens the hypothesis of an association between cigarette smoking and bladder cancer.

In this report, temporal trends in the occurrence of bladder cancer in the Netherlands are summarised. There is no national cancer registry in the Netherlands from which incidence data can be obtained as yet. Mortality statistics from the Dutch Central Bureau of Statistics from 1955 to 1988 are therefore used for analysis. Statistical modelling is used to examine whether temporal variations in rates are attributable to a cohort effect and/or to a calendar period effect. The results from this modelling are also used to obtain some indication of a change in temporal trend in the near future.

Methods

In the Netherlands, the Central Bureau of Statistics (CBS) has registered underlying causes of death

since 1900. The number of men and women with bladder cancer as the cause of death, as well as age- and sex-specific numbers of the Dutch population, were abstracted from the annual publications of the CBS for the years 1955 to 1988 (CBS, 1980, 1990). In this period, 4 revisions of the International Classification of Diseases were used. For the sixth and seventh revisions, ICD code 181.0 and for the eighth and ninth revisions ICD code 188 were used as definitions of bladder cancer. Only a small difference exists between the ninth revision and the former 3, using these codes: in the ninth revision the urachus is coded under "bladder cancer", whereas in the former editions the urachus is coded under "other urinary organs".

For statistical analysis the numbers of bladder cancer deaths were organised according to 5-year age groups and 5-year calendar periods of registration. Rates per 10⁵ person-years based on these numbers are illustrated in Tables 1 and 2. Ages under 35 were ignored because of the rarity of mortality from the disease under this age. The

Table 1 Age-specific Bladder Cancer Mortality Rates per 100,000 Man-years in the Netherlands, 1955-1988

Age (years)	Calendar year of mortality						
	1955-59	1960-64	1965-69	1970-74	1975-79	1980-84	1985-88
35-39	0.1	0.3	0.4	0.2	0.1	0.2	0.4
40-44	0.8	0.6	0.9	0.9	0.6	0.4	0.6
45-49	2.4	1.9	2.3	2.1	2.7	1.8	1.8
50-54	4.5	6.7	5.1	5.7	5.7	4.0	4.8
55-59	10.3	10.7	12.0	11.8	11.2	11.6	9.9
60-64	15.6	20.2	23.7	24.6	22.4	23.5	23.3
65-69	22.7	31.9	36.8	42.1	42.8	44.2	39.6
70-74	42.6	47.2	59.0	66.5	71.7	68.6	68.4
75-79	66.8	67.9	80.2	93.9	95.5	113.2	117.5
80-84	73.6	107.4	110.0	128.7	139.8	155.2	176.9

The step line indicates the 1910 birth cohort.

Table 2 Age-specific Bladder Cancer Mortality Rates per 100,000 Woman-years in the Netherlands, 1955-1988

Age (years)	Calendar year of mortality						
	1955-59	1960-64	1965-69	1970-74	1975-79	1980-84	1985-88
35-39	0.1	0.1	0.3	0.1	0.2	0.2	0.3
40-44	0.6	0.3	0.2	0.4	0.5	0.6	0.2
45-49	0.4	0.8	0.9	0.8	0.6	0.7	0.3
50-54	1.6	1.4	1.3	1.7	0.7	1.8	1.7
55-59	3.0	2.4	2.7	2.9	2.5	2.1	3.2
60-64	5.3	5.6	4.9	3.9	4.3	4.6	4.6
65-69	9.0	8.6	9.2	6.8	6.7	7.3	7.8
70-74	15.9	13.9	14.8	15.3	14.1	13.1	13.9
75-79	25.4	32.5	26.7	24.4	24.3	24.9	26.2
80-84	39.8	39.5	41.2	46.1	37.9	37.2	48.2

The step line indicates the 1910 birth cohort.

highest age group (85+) was also ignored because no specific period of birth can be defined for this birth cohort. Birth cohorts were defined by combining age and calendar periods (see step lines in Tables 1 and 2).

To compare bladder cancer mortality rates in different calendar periods, adjustment for the change in age distribution of the Dutch population is necessary. Thus mortality rates in 7 successive calendar periods from 1955 to 1959 to 1985 to 1988 were age-standardised to the European standard population. This means that for each calendar period we calculated what the mortality rate in this standard population with a constant age distribution would have been if it had experienced the same age-specific mortality as the Dutch population.

To estimate the separate effects of age, calendar period and birth cohort on trend in mortality, a simultaneous analysis of these factors was performed by using a statistical model. A simple model is the multiplicative one, where the mortality for a specific age-period-cohort combination is, apart from random fluctuation, described as a product of these 3 factors (Habbema, 1981):

$$Y_{apc} = \alpha_a \pi_p \tau_c$$

where Y_{apc} is mortality rate for age group a , born in period c , as experienced during calendar period p ; α_a is a factor describing the effect on mortality of age group a ; π_p is a factor describing the effect on

mortality of calendar period p ; τ_c is a factor describing the effect on mortality of birth cohort c .

Such a model is also called a log-linear model, because by taking the logarithm ($\ln$) on both sides of the equality sign one obtains a linear model:

$$\ln(Y_{apc}) = \ln \alpha_a + \ln \pi_p + \ln \tau_c$$

The age factor, period factor and cohort factor are fitted so that their products in all age period groups in Tables 1 and 2 are as close to the observed rates as possible. The statistical procedure used here for estimating the factors is the maximum likelihood method. The software package GLIM was used for computations.

To test the goodness-of-fit of the models with the observed mortality rates as well as to test the models against each other, the χ^2 approximation to the $-2 \ln$ (likelihood ratio) was used. For an explanation of log-linear models for the analysis of temporal variation in cancer, 2 reports are recommended (Clayton and Schifflers, 1987a and b).

Results

From 1955 to 1959 the age-standardised bladder cancer mortality rates per 10^5 person-years were 7.5 in men and 2.9 in women. From 1985 to 1988 these rates were 12.4 and 3.0 respectively (Fig. 1). The increasing temporal trend in men seems to originate from a higher risk of dying from bladder

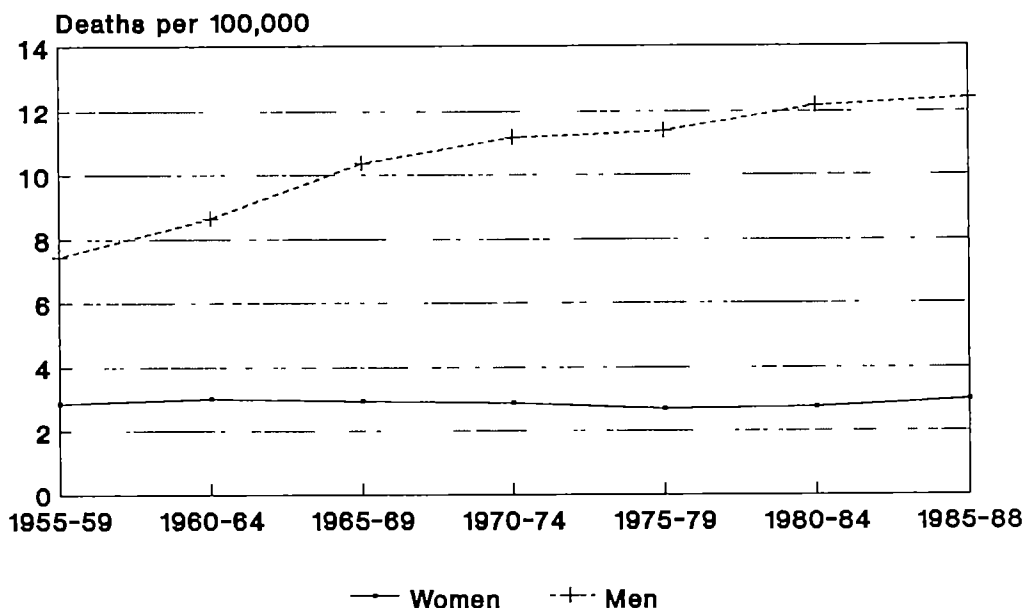


Fig. 1 Trend in bladder cancer mortality in the Netherlands between 1955 and 1988 (age-standardised to the European standard population).

cancer in the 4 oldest age groups (Fig. 2). In men over 65 years of age the rates doubled in this 34-year time period. In women such an increase was not seen in the older age groups (Fig. 3). Mortality rates were stable over time in all age groups, reflecting a situation of no temporal trend.

Since male rates did not rise in all age groups, this suggests that a calendar period effect is not

responsible for the increasing trend. Statistical modelling of the rates in men yields the results summarised in Table 3. Model 1 is the model which assumes that there is no temporal trend in male bladder cancer mortality. Since an increasing trend exists in male bladder cancer mortality, this model gives a very poor description of the data. This is reflected in the relatively large deviance from the

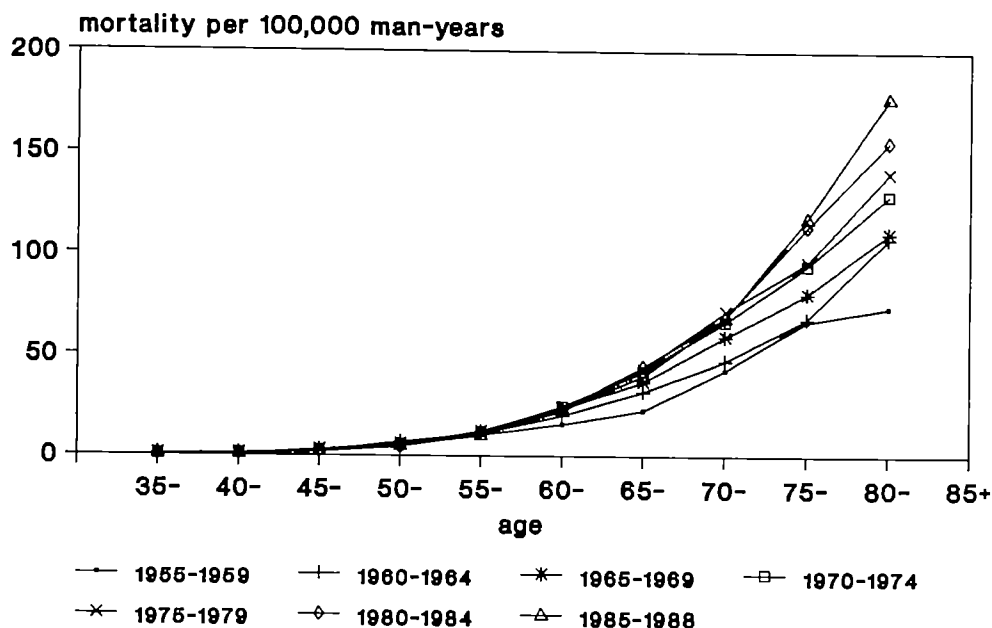


Fig. 2 Age-specific bladder cancer mortality in Dutch men according to registration period.

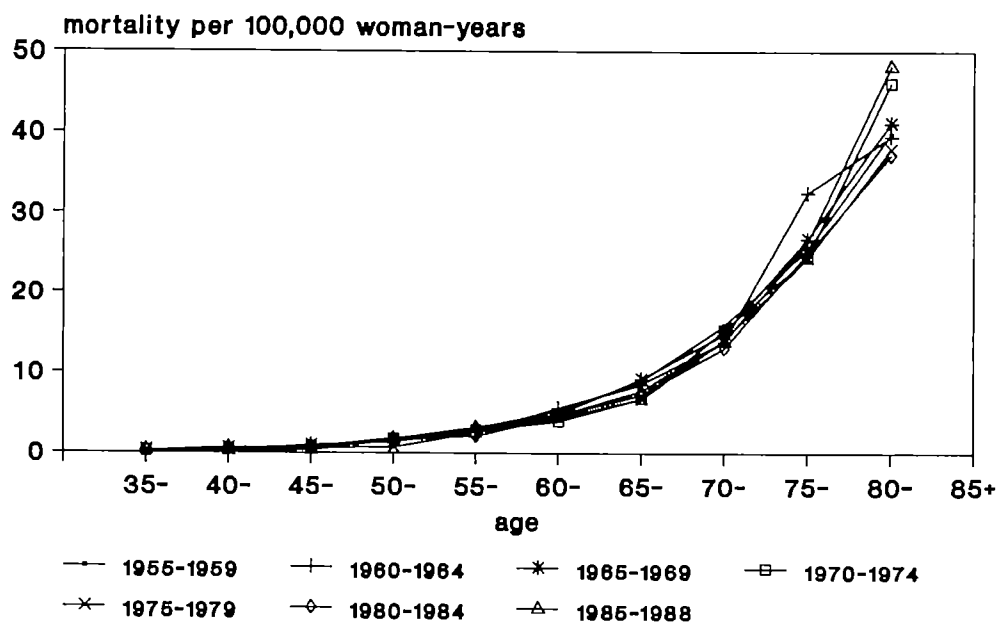


Fig. 3 Age-specific bladder cancer mortality in Dutch women according to registration period.

Table 3 GLIM Statistics for Bladder Cancer Mortality in the Netherlands

Males	Model	Deviance	df	P
	(1) Age*	555.2	60	<0.001
	(2) Age + drift†	234.6	59	<0.001
	(3) Age + period	182.9	54	<0.001
	(4) Age + cohort	53.3	45	0.19
	(5) Age + period + cohort	37.8	40	0.57
	Model (4) vs model (5)	15.5	5	0.01

*The AGE model describes the situation in which rates are predicted by age factors only and represents the null hypothesis of no temporal variation.

†The AGE + DRIFT model is a model with temporal trend in which no distinction can be made between period effects (model 3) and cohort effects (model 4).

model compared with the number of degrees of freedom (df). If a model gives a good description of the observed rates the deviance from the model is about the same as the number of df and far from significant. In that situation the *P* value is close to 0.50. Since the *P* value in the age-only model is very small the model does not hold, which means that there is some temporal variation.

The simplest model to describe temporal variation is the so-called age-drift model (Clayton and Schifflers, 1987a). If this age-drift model gives a good description of the data, then a temporal trend exists for which no distinction can be made between period effects and cohort effects (model 2). However, the age-drift model does not hold either, since

there is large deviance from the model. The next 2 models to consider are the age-period model (model 3) and the age-cohort model (model 4). Obviously the variation in bladder cancer mortality rates is much better explained by cohort effects than by calendar period effects. Unlike the age-period model, the age-cohort model provides an adequate description of the data (there is no significant deviance from the model: *P* = 0.19).

The parameter estimates τ_c from the age-cohort model are interpretable as relative risks between 2 birth cohorts. Defining the 1910 cohort as a reference group, the relative risks of bladder cancer mortality in Dutch men are illustrated in Figure 4. It can be seen that mortality increased until this 1910 cohort. Figure 4 also shows that the relative risk of dying from bladder cancer decreases for successive younger birth cohorts after the 1910 cohort. For example, compared with men born in 1910, the risk of dying from bladder cancer for men (of the same age) born in 1940 is only 67%. The standard graphical presentation of temporal trends (Fig. 1) fails to identify this decreasing risk experienced by recent cohorts. Next to a cohort effect, a calendar period effect cannot be ruled out since there exists no significant deviance from the age-period-cohort model (model 5) as well (*P* = 0.57). Compared with the age-cohort model this full age-period-cohort model gives a significantly better fit to the observed rates (*P* = 0.01). It is hard to assess, however, how great this calendar period effect is,

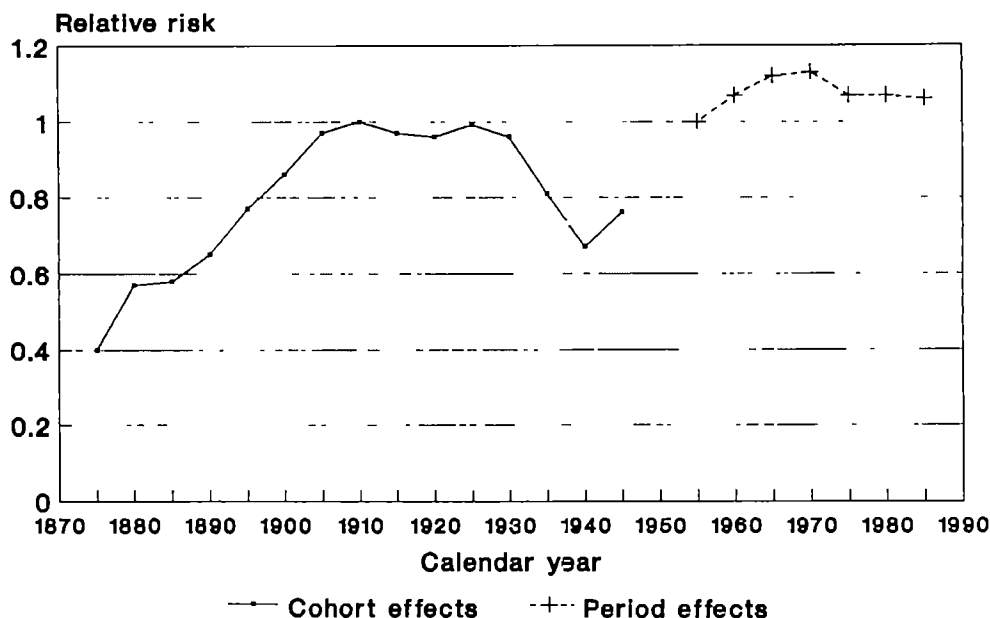


Fig. 4 Relative risk of male bladder cancer mortality in the Netherlands according to year of birth and registration period.

because there is a major difficulty in the use of the age-period-cohort model. Knowing any 2 of age at death, year of birth and year of death fixes the third. Thus the 3 variables are not independent. A consequence of this relationship is that the solution from the model is not unique, although each solution produces the same fitted rates (Osmond, 1985). To overcome this problem one of all solutions from the age-period-cohort model was chosen in which the cohort effect is the same as in model 4: the age-cohort model. Through this, the period effect is identified. Taking the first calendar period (1955-59) as reference, the relative risks of dying from bladder cancer in more recent calendar periods appear to be close to 1 (Fig. 4). Although the inclusion of a period effect describes the observed rates significantly better than the age-cohort model, the period effect is not relevant quantitatively.

Discussion

When the incidence rates of a particular cancer are changing with time, the first question to be asked is whether the change represents a real change in disease occurrence or simply a change in diagnostic/registration practice or acuity. In the case of trends in mortality rates also, a change in prognosis is possible. Examples of changes in diagnostic/registration practice might be changes in (1) the definition of the malignancy, (2) histological confirmation, (3) autopsy rate and (4) diagnostic accuracy. Differences or changes in applied therapeutics are another possible explanation of trends in mortality.

As stated before, there were no important changes in the definition of bladder cancer in the 4 revisions of the ICD used by the Dutch Central Bureau of Statistics. Furthermore, changes in histological confirmation and autopsy rate will presumably not be very important for bladder cancer. A change in histological confirmation is more relevant in the case of cancers that can be classified under 2 or more different rubrics, such as lymphomas of the gastrointestinal tract, or when specific histological subtypes of a tumour are studied. A change in histological confirmation is also important when cancer sites are studied to which other cancers frequently metastasise, e.g. lung and liver cancer. A change in autopsy rate is more relevant if tumours are studied that may remain latent, such as prostate cancer.

Changes in diagnostic and registration accuracy probably have less impact on bladder cancer mortality than on bladder cancer incidence. One of the most important registration problems in bladder

cancer incidence is the classification of papillomas. Because of the absence of criteria which allow a clear distinction between papillomas with benign behaviour and those that will eventually manifest malignancy, for the last 2 decades non-invasive papillomas were treated more frequently. This change in policy may bias bladder cancer incidence rates but will have less effect on bladder cancer mortality.

In recent decades, survival rates of patients suffering from bladder cancer have shown a tendency to increase. In Alberta, Canada, the 5-year survival rate for men increased from 52% in 1964 to 65% in 1988 (Berkel *et al.*, 1990). However, if this increase is due to an increase in the proportion of superficial bladder cancers (pTa and pT1), the apparent improvement in treatment results may have little effect on mortality statistics (Staszewski, 1980). It is not known whether this is the case in the Netherlands.

If one is satisfied that a change in incidence or mortality is not an artefact but real, it is interesting to identify the environmental or other changes that might be responsible. In identifying the factors responsible for the change in rates it is helpful to differentiate calendar period and birth cohort patterns in the data by means of statistical modelling (Day and Charnay, 1982). A calendar period model suggests an immediate (or a fixed delayed) effect upon incidence (or mortality) which is constant across all age groups. A birth cohort model suggests an effect which affects rates in a specified generation equally throughout life.

Whereas no temporal trend was observed in female bladder cancer mortality in the Netherlands, for male bladder cancer mortality the increasing trend was found to be due mainly to a cohort effect. This difference between male and female trends in mortality is seen all over the world (Armstrong and Doll, 1974; Staszewski, 1980; La Vecchia *et al.*, 1990a). The fact that there is no temporal trend in mortality in women also lends support to the idea that the temporal trend in men is not caused by an artefact.

The cohort effect in men shows an increasing trend for successive birth cohorts until those born after 1910. The same was reported for England and Wales male mortality by Armstrong and Doll (1974). In Italian male mortality the increasing trend lasts at least until the 1935 cohort (Clayton and Schiffers, 1987a).

Almost all authors correlate the cohort effect with the rise in cigarette consumption, the best known risk factor in bladder cancer. Differences in

trends in males and females could also be attributed to smoking (Staszewski, 1980; Roush *et al.*, 1985; Devesa *et al.*, 1987). Other risk factors may also have an effect on bladder cancer occurrence. The most important of these potential risk factors is exposure to carcinogenic dye-stuffs, *e.g.* β -naphthylamine and benzidine, in certain occupations. However, although the relative risk of this factor is perhaps reasonably large (4.6 according to La Vecchia *et al.*, 1990b), the effect on trends in occurrence will probably be small because the proportion of the population that is exposed to these dyes is small.

If cigarette consumption is indeed the aetiological factor responsible for the increasing bladder cancer mortality and incidence rates, then presumably trends will decline in the near future, since more and more people will be life-long non-smokers. For example, in the Netherlands there has been a sharp fall in the proportion of smokers among men from 90% in 1958 to 44% in 1984. Such a decline is not yet visible in the more or less standard method of illustration of temporal trends (Fig. 1). When it can be expected is hard to tell. Among other factors, this depends especially on the proportion of the disease attributable to smoking and the length of the latent period of bladder cancer. Considering the relative risks for successive male birth cohorts (Fig. 4), perhaps the decline will be seen within the next decade when more cohorts with a decreasing relative risk will reach ages over 70. In this respect, it is also illustrative that the incidence of lung cancer and laryngeal cancer is already declining in Scotland (Boyle and Robertson, 1987), since the length of the latent period for these smoking-related cancers is presumed to be shorter than that for bladder cancer. Perhaps the relatively long latency for bladder cancer is also the reason why, contrary to lung cancer mortality in females, which has been rising steeply since 1980 (Verbeek *et al.*, 1985), an increasing trend for bladder cancer mortality is not seen in Dutch women.

References

- Armstrong, B. and Doll, R. (1974). Bladder cancer mortality in England and Wales in relation to cigarette smoking and saccharin consumption. *Br. J. Prev. Soc. Med.*, **28**, 233–240.
- Berkel, J., Anderson, W. A., Hanson, J. *et al.* (1990). *Incidence, Survival and Distribution of Cancer in Alberta 1964 to 1988*. Edmonton: Alberta Cancer Board.
- Boyle, P. and Robertson, C. (1987). Statistical modelling of lung cancer and laryngeal cancer incidence in Scotland, 1960–1979. *Am. J. Epidemiol.*, **125**, 731–744.
- Central Bureau of Statistics (1980). *Mortality by Cause of Death, 1950–1977*. (In Dutch). 's-Gravenhage: Staatsuitgeverij.
- Central Bureau of Statistics (1990). *Mortality by Cause of Death, Age and Sex in the Year (1978–) 1988 Series A1*. (In Dutch). 's-Gravenhage: Staatsuitgeverij.
- Clayton, D. and Schifflers, E. (1987a). Models for temporal variation in cancer rates 1: Age-period and age-cohort models. *Stat. Med.*, **6**, 449–467.
- Clayton, D. and Schifflers, E. (1987b). Models for temporal variation in cancer rates 2: Age-period-cohort models. *Stat. Med.*, **6**, 469–481.
- Day, N. E. and Charnay, B. (1982). Time trends, cohort effects, and aging as influence on cancer incidence. In *Trends in Cancer Incidence Causes and Practical Implications*, ed. Magnus, K. Pp. 51–65. Washington: Hemisphere.
- Devesa, S. S., Silverman, D. T., Young, J. L. *et al.* (1987). Cancer incidence and mortality trends among whites in the United States, 1947–84. *J. Natl. Cancer Inst.*, **79**, 701–770.
- Doll, R., Payne, P. and Waterhouse, J. (1966). *Cancer Incidence in Five Continents*. Volume 1. Berlin: Springer-Verlag.
- Habbema, J. D. F. (1981). Simultaneous analysis of age-, birth cohort-, and time period effects. In *Preliminaries for Evaluation of Breast Cancer Screening*, ed. van Putten, D. J., Habbema, J. D. F., van Oortmarssen, G. J. *et al.* Chapter 3, pp. 6–17. Rotterdam: Erasmus University.
- Hoover, R. and Cole, P. (1973). Temporal aspects of occupational bladder cancer carcinogenesis. *N. Engl. J. Med.*, **288**, 1040–1043.
- La Vecchia, C., Negri, E., Decarli, A. *et al.* (1990a). Cancer mortality in Italy: an overview of age-specific and age-standardised trends from 1955–1984. *Tumori*, **76**, 87–166.
- La Vecchia, C., Negri, E., D'Avanzo, B. *et al.* (1990b). Occupation and the risk of bladder cancer. *Int. J. Epidemiol.*, **19**, 264–268.
- Morrison, A. S. and Cole, P. (1982). Urinary tract. In *Cancer Epidemiology and Prevention*, ed. Schottenfeld, D. and Fraumeni, J. F. Chapter 54, pp. 925–937. Philadelphia: Saunders.
- Muir, C., Waterhouse, J., Mack, T. *et al.* (1987). *Cancer Incidence in Five Continents*. Volume 5. Lyon: International Agency for Research on Cancer.
- Osmond, C. (1985). Using age, period and cohort models to estimate future mortality rates. *Int. J. Epidemiol.*, **14**, 124–129.
- Roush, G. C., Holford, T. R., Schymura, M. J. *et al.* (1987). *Cancer Risk and Incidence Trends. The Connecticut Perspective*. Washington: Hemisphere.
- Roush, G. C., Schymura, M. J., Holford, T. R. *et al.* (1985). Time period compared to birth cohort in Connecticut incidence rates for twenty-five malignant neoplasms. *J. Natl. Cancer Inst.*, **74**, 779–788.
- Staszewski, J. (1980). Cancer of the urinary bladder: international mortality patterns and trends. *World Health Stat. Q.*, **33**, 27–41.
- Verbeek, A. L. M., Peeters, P. H. M. and Sturmans, F. (1985). Is the peak of the lung cancer epidemic in the Netherlands visible already? (In Dutch). *Ned. Tijdschr. Geneesk.*, **129**, 2365–2369.

The Authors

- L. A. L. M. Kiemeny, MSc, Epidemiologist, University of Nijmegen and Comprehensive Cancer Centre IKO, Nijmegen.
- A. L. M. Verbeek, MD, PhD, Epidemiologist, University of Nijmegen.
- P. J. Nelemans, MD, Epidemiologist, University of Nijmegen.
- J. A. Witjes, MD, Urologist, University Hospital Nijmegen.
- H. Straatman, MSc, Statistician, Department of Epidemiology, University of Nijmegen.
- Requests for reprints to: L. A. L. M. Kiemeny, Department of Epidemiology, University of Nijmegen, Verlengde Groenestraat 75, 6525 EJ Nijmegen, The Netherlands.

Is Pre-operative Imaging of the Urinary Tract Worthwhile in the Assessment of Prostatism?

A. G. WILKINSON and S. R. WILD

Department of Radiology, Western General Hospital, Edinburgh

Summary—The reports of routine pre-operative imaging investigations performed on patients presenting with symptoms of uncomplicated benign prostatic hypertrophy were compared with management decisions and clinical outcome. In 175 patients with prostatism no urological abnormality which altered management was discovered on plain films of the abdomen and pelvis and ultrasound of the urinary tract which were performed routinely.

Post-micturition residual volume (PMRV), estimated by ultrasound, was compared with the maximum urine flow rate (Q max) in 57 patients. PMRV showed negative correlation with Q max. Both high PMRV and low Q max were associated with the urologist's decision to operate, but multiple logistic regression revealed that ultrasound residual volume was not a significant predictor of operation when adjusted for Q max. Urologists in this hospital therefore use flow rates as the primary indication of the need to operate.

We suggest that no routine pre-operative imaging need be performed in patients presenting with prostatism.

Imaging of the urinary tract in patients presenting with prostatism is controversial and several workers (Bruskewitz *et al.*, 1982; Fidas *et al.*, 1987; de Lacey *et al.*, 1988; Timoney *et al.*, 1989) have questioned the need for intravenous urography or ultrasonography to detect abnormalities of the renal tract or assess PMRV. Jensen *et al.* (1988a) suggested that a Q max > 15 ml/s indicated the likelihood of a poor post-operative outcome. Wilkinson and Wild (1992) showed a wide variation in routine pre-operative imaging in different urological centres throughout Britain. The aims of this study were to determine the effect on management of abnormalities detected on routine pre-operative imaging of the urinary tract, to compare estimation of PMRV by ultrasound with measurement of Q max, and to relate these factors to the clinical outcome in order to determine the value of these investigations to the urologists in this unit.

Patients and Methods

The study group comprised 175 consecutive patients with prostatism, aged between 31 and 88 years, who were referred to this department by urologists. Patients in acute retention and those with haematuria were excluded. All patients presenting to the urologists with uncomplicated prostatism underwent routine imaging; this included ultrasound of the urinary tract with a full bladder, ultrasound estimation of the bladder volume immediately after micturition (calculated as $0.6 \times \text{oblique length} \times \text{height} \times \text{width}$) and plain films of the abdomen and pelvis (KUB) as proposed by Fidas *et al.* (1987). All ultrasound examinations were performed by radiologists, usually of consultant grade, although some were performed by registrars and senior registrars under consultant supervision. The urologists' decision to operate was made on clinical grounds, with the results of imaging and the PMRV estimated by ultrasound available. Urologists requested peak flow rate measurements in about half of the patients considered for prostatectomy, presumably those in

whom there was clinical doubt as to the significance of symptoms of obstruction.

All reports were examined in order to determine the number of abnormalities detected on routine pre-operative imaging of the urinary tract. The records of all patients with abnormal reports were examined to determine whether these imaging investigations led to a change in patient management.

The records of 116 patients were examined to determine the results of other investigations performed or requested by the urologists and to record the clinical outcome. These were divided into 3 groups: ultrasound volumes 0–51 ml ($n=38$), 51–200 ml ($n=40$) and over 200 ml ($n=38$). Long waiting lists for prostatectomy resulted in some of the later patients in the study still waiting either for operation or a clinical decision at the time of writing, thereby reducing the numbers included in this part of the study.

Results

The PMRV measured by ultrasound ranged from zero to more than 1130 ml (the maximum that could be measured because of limitations imposed by the size of the ultrasound sector); the mean was 140 ml.

Of 175 patients with prostatism whose reports were examined for abnormality detected on routine ultrasound examination, 24 were found to have 25 abnormalities (Table 1). In none of these was management altered solely because of the demonstration of a previously unknown urinary tract abnormality. Renal calculi were identified in 4 of the 175 patients on plain film examination; in none of these was the clinical management altered.

Of the 116 patients whose notes were examined for details of other investigations and clinical management by the urologists, 57 had the peak

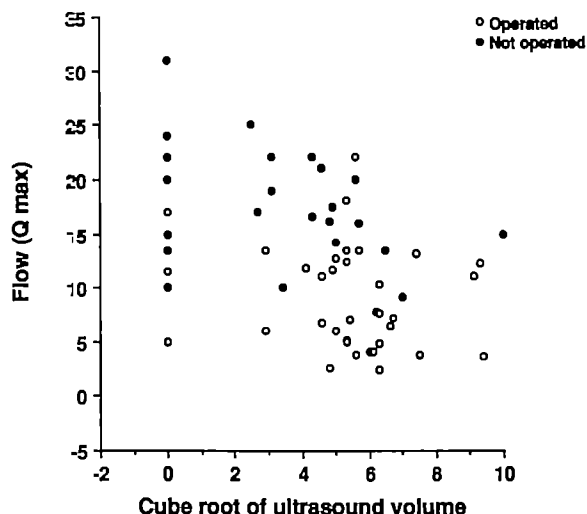


Fig. Plot of cube root of ultrasound volume and maximum flow rate with operative decision.

urinary flow rate ($Q_{\max}$) measured and a negative correlation of $Q_{\max}$ and ultrasound residual volume was found (Kendall rank correlation coefficient = -0.31 , $P < 0.01$). A total of 59 patients were scheduled for operation and 38 had undergone surgery at the time of writing; 34 patients underwent prostatectomy (33 transurethrally and 1 by retro-pubic prostatectomy); 27 proved to have benign hyperplasia and 7 prostatic malignancy. Three patients underwent urethrotomy for stricture and 1 had a bladder neck resection. Wilcoxon rank sum tests showed that the decision to operate was associated very significantly ($P < 0.001$) with both PMRV and $Q_{\max}$. High PMRV and low $Q_{\max}$ tended to occur in the operated group (Fig.). However, multiple logistic regression revealed that PMRV did not provide a significant prediction of

Table 1 Abnormalities Detected on Routine Pre-operative Ultrasound in 175 Patients

Abnormality	No. of abnormalities	Effect on management
Hydronephrosis	11	1 operation delayed (renal failure)
? bladder tumours	4	3 false positives 1 no action
? renal tumours	3	No action
? prostatic tumours	2	1 already clinically diagnosed 1 false positive at operation
Crossed fused renal ectopia	2	No action
Aortic aneurysms	2	1 repaired prior to prostate surgery
Bladder diverticulum	1	No action
Total	25	

Table 2 Clinical Outcome in Relation to Residual Volume

<i>US residual volume (ml)</i>	<i>No.</i>	<i>Listed for operation (%)</i>	<i>Mean wait for operation (weeks)</i>	<i>Mean weight of benign prostate resected (g)</i>
< 50	38	11 (29)	29	34 (n=6)
51-200	40	20 (50)	28	25 (n=6)
> 200	38	28 (73)	18	15 (n=11)

operation when adjusted for flow rate. It therefore appears that urologists in this hospital are using the peak urinary flow rate as the primary indication of the need to operate. Patients with large residual volumes tended to come to operation earlier and have less prostatic tissue resected (Table 2). Although fewer patients in whom peak urinary flow rates had been measured were available for analysis, it did not seem that patients with low flow rates (<10 ml/s) were admitted earlier than those with high flow rates (>10 ml/s), as both groups waited a mean of 22 weeks between ultrasound examination and operation.

Of the 27 patients who completed follow-up after prostatectomy for benign hyperplasia, only 1 had an unsatisfactory outcome and complained of incontinence and impotence for more than a year after the operation. This patient had a pre-operative residual volume of 25 ml and no flow rate measurement was performed.

Discussion

The aims of this study were to determine whether routine imaging of the urinary tract is worthwhile in the pre-operative assessment of patients who present with symptoms of uncomplicated benign prostatic hyperplasia, and to assess whether measurement of the PMRV influenced the urologist in his decision to proceed to prostatectomy. Transurethral resection of the prostate (TUR) has an average mortality of 1.6% (Neal, 1990) and subjective satisfaction rates of 79% were reported by Neal *et al.* (1989) and 86% by McLoughlin *et al.* (1990). The selection of patients for this procedure is therefore of great importance.

A recent survey of urologists to determine current practice in the pre-operative investigation of patients considered for prostatectomy has shown wide variation between urological centres (Wilkinson and Wild, 1992). The routine pre-operative imaging of the upper urinary tract in prostatism has been reviewed by de Lacey *et al.* (1988), who concluded

that neither routine urography nor ultrasound appeared to be justified. Hydronephrosis is the commonest abnormality detected on routine screening of the urinary tract (Fidas *et al.*, 1987) but even gross hydronephrosis with impairment of renal function responds to conventional management (*i.e.* prostatectomy), with biochemical improvement in 50% of patients (Nissenkorn *et al.*, 1988). It is therefore unlikely that the detection of hydronephrosis will alter clinical management, particularly if there are no biochemical abnormalities.

In the present study no alteration in clinical management was made purely on the basis of routine pre-operative imaging of the urinary tract in 175 patients. Of 11 patients reported to have hydronephrosis on ultrasound, only 1 had a raised urea level and it was the biochemical rather than the imaging investigation that altered surgical management, since operation was delayed until biochemical parameters had returned towards normal values following catheterisation. Several months after operation the urea and creatinine remained moderately elevated but the hydronephrosis had largely resolved on repeat ultrasound examination.

No patient was proved to have a renal tumour, although 3 were suspected on initial ultrasound and DMSA scans were suggested in the ultrasound reports of these patients. No further investigation of these patients was requested by the urologists, suggesting that the radiologists' reports had been either unread or unheeded. Brooks (1988) showed that the detection of asymptomatic renal cancers in patients with prostatism is a rare occurrence, with only 5 tumours detected in 3128 patients (0.16%) by routine IVU without nephrotomography. Four patients were noted to have an irregular bladder wall, suggesting malignant infiltration, although in none of 3 patients undergoing cystoscopy was a bladder tumour confirmed, and the fourth was discharged from the clinic without further investigation. Two prostatic malignancies were suspected

at ultrasound: 1 was diagnosed clinically prior to ultrasound and confirmed on routine transurethral resection and the other was shown to be a false positive at operation. Of 2 patients with aortic aneurysms, 1 was already known and surgery was not planned because of the patient's advanced age. The other was diagnosed *de novo* on ultrasound examination and the patient had a repair prior to transurethral resection. Imaging of the entire abdomen was not routinely performed during pre-operative assessment for prostatectomy, so that this must be classified as a chance finding. The aneurysm should have been detected clinically by abdominal palpation.

The value of PMRV estimation in pre-prostatectomy assessment was questioned by Bruskewitz *et al.* (1982), who showed a wide variation of PMRV in individual patients on different occasions and poor correlation with symptomatology, cystoscopic findings and urodynamic result. There is controversy about the significance of a large PMRV. Neal *et al.* (1987) claimed that high PMRV correlated with high urethral resistance but not weak voiding pressures, whereas Abrams and Griffiths (1979) and Anderson (1982) claimed that PMRV was related to abnormality of bladder function. Jensen *et al.* (1988b), in a urodynamic study, showed that PMRV had no predictive value for post-operative outcome. No previous imaging study has examined the value of imaging PMRV in predicting the need for or the outcome of operation, although Fidas *et al.* (1987) commented that knowledge of a large residual volume may influence surgical management. Powell *et al.* (1980) claimed that a large PMRV predisposed to acute urinary retention. None of the study patients developed acute retention whilst on the waiting list for surgery.

The results of this study show that urologists in this institution are more likely to operate, and to do so earlier, in patients with a large PMRV. However, in those patients with Q max estimation, urologists used this in preference to PMRV when predicting the need for operation. This follows the recommendation of Jensen *et al.* (1988a), who suggested a cut-off value of 15 ml/s above which patients were at risk of a less favourable outcome following surgery. McLoughlin *et al.* (1990) showed that a screening Q max of 12 ml/s or less was associated with urodynamic evidence of obstruction in 95% of cases.

The cost of routine pre-operative imaging is considerable. Plain films of the abdomen and pelvis cost approximately £20 and ultrasound of the renal tract approximately £80. Over 35,000 prostatecto-

mies are performed in the UK each year. Even if routine imaging were confined only to those patients presenting with prostatism who came to surgery, the cost to the health service would be in the region of £3.5 million annually. In this institution approximately half of the patients investigated for prostatism required operation. If this represents normal practice, the overall cost to the health service would be 2 × £3.5 million, *i.e.* £7 million. In other institutions the proportion of patients investigated who require surgery may be lower, in which case the potential savings resulting from abandoning routine imaging would be even greater.

In conclusion, we suggest that routine imaging of the urinary tract prior to prostatectomy rarely alters clinical management and could be discontinued. The PMRV is of limited use in the assessment of prostatism, and flow rates are considered more relevant in predicting the need for operation. Routine measurement of PMRV should be abandoned. If needed, the PMRV can be readily assessed on a KUB film (Morewood and Scally, 1986; Wilkinson and Wild, unpublished data). Estimation of blood urea or creatinine and a flow rate would appear to be the only investigations required to aid clinical management. The financial implications of discontinuing routine pre-operative imaging are considerable.

Acknowledgement

We are grateful to Dr R. Elton, Medical Statistics and Computing Department, University of Edinburgh, for performing the statistical analysis.

References

- Abrams, P. H. and Griffiths, D. J. (1979). The assessment of prostatic obstruction from urodynamic measurements and residual urine. *Br. J. Urol.*, **51**, 129–134.
- Anderson, J. T. (1982). Prostatism III. Detrusor hyperreflexia and residual urine. Clinical and urodynamic aspects and the influence of surgery on the prostate. *Scand. J. Urol. Nephrol.*, **16**, 25–30.
- Brooks, A. P. (1988). Prostatism, intravenous urography and asymptomatic renal cancer. *Br. J. Urol.*, **62**, 1–3.
- Bruskewitz, R. C., Iverson, P. and Madsen, P. O. (1982). Value of post void residual urine determination in evaluation of prostatism. *Urology*, **20**, 602–604.
- de Lacey, G., Johnson, S. and Mee, D. (1988). Prostatism: how useful is imaging of the urinary tract? *Br. Med. J.*, **296**, 965–967.
- Fidas, A., Mackinlay, J. Y., Wild, S. R. *et al.* (1987). Ultrasound as an alternative to intravenous urography in prostatism. *Clin. Radiol.*, **38**, 479–482.
- Jensen, K. M., Jorgensen, J. B. and Mogensen, P. (1988a). Urodynamics in prostatism. I. Prognostic value of uroflowmetry. *Scand. J. Urol. Nephrol.*, **22**, 109–117.

- Jensen, K. M., Jorgensen, J. B. and Mogensen, P. (1988b). Urodynamics in prostatism III. Prognostic value of medium fill water cystometry. *Scand. J. Urol. Nephrol. (Suppl.)*, **114**, 78-83.
- McLoughlin, J., Gill, K., Abel, P. D. *et al.* (1990). Symptoms versus flow rates versus urodynamics in the selection of patients for prostatectomy. *Br. J. Urol.*, **66**, 303-305.
- Morewood, D. J. W. and Scally, J. K. (1986). An evaluation of the post-micturition radiograph following intravenous urography. *Clin. Radiol.*, **37**, 499-500.
- Neal, D. E. (1990). Prostatectomy: an open or closed case. *Br. J. Urol.*, **66**, 449-454.
- Neal, D. E., Ramsden, P. D., Sharples, L. *et al.* (1989). Outcome of elective prostatectomy. *Br. Med. J.*, **299**, 762-767.
- Neal, D. E., Styles, R. A., Powell, P. H. *et al.* (1987). Relationship between detrusor function and residual urine in men undergoing prostatectomy. *Br. J. Urol.*, **60**, 560-566.
- Nissenkorn, I., Savion, M. and Servadio, C. (1988). Renal and bladder function recovery after prostatectomy in patients with chronic residual urine of above 1,000 ml. *Eur. Urol.*, **14**, 434-436.
- Powell, P. H., Smith, P. J. B. and Feneley, R. C. L. (1980). The identification of patients at risk from acute retention. *Br. J. Urol.*, **52**, 520-522.
- Timoney, A. G., Payne, S. R., Davies, L. A. L. *et al.* (1989). The "plain film" bladder shadow in outflow obstruction: as accurate a discriminant of residual urine as ultrasound. *Br. J. Urol.*, **63**, 363-366.
- Wilkinson, A. G. and Wild, S. R. (1992). Survey of urological centres and review of current practice in the pre-operative assessment of prostatism. *Br. J. Urol.*, **70**, 43-45.

The Authors

A. G. Wilkinson, MA, MRCP, FRCR, Senior Registrar.
S. R. Wild, FRCR, FRCPE, Consultant Radiologist.

Requests for reprints to: A. G. Wilkinson, Department of Radiology, Western General Hospital, Crewe Road, Edinburgh EH4 2XU.

Urinary Flow Rates in Patients with Benign Prostatic Hypertrophy following Treatment with Alfuzosin

P. TEILLAC, M. C. DELAUCHE-CAVALLIER, P. ATTALI and the DUALF Group

Hôpital St Louis and Synthélabo Recherche, Paris, France

Summary—In order to document further the onset of action of alfuzosin, a selective alpha-1 blocker, 93 symptomatic patients with benign prostatic hypertrophy were randomly allocated to a single oral dose of either alfuzosin 1.25 mg or 2.5 mg, or placebo, after a 1-week placebo lead-in period. The effects on flow rates were assessed 1 h 30 min after administration. Peak and mean flow rates were significantly increased in the alfuzosin groups, as compared with placebo, in a dose-dependent manner. After a single intake of placebo, the mean values of these 2 parameters showed little change. The effect on the cardiovascular system (heart rate and blood pressure) was mild. This study indicates that the action of alfuzosin is already present 1 h 30 min after administration.

There has been increasing agreement in recent years on the usefulness of alpha-1 blockers in the treatment of micturition disorders related to benign prostatic hypertrophy (BPH) (Caine, 1986). Human adenoma and the prostatic capsule have been shown to be rich in alpha- adrenergic receptors which, when stimulated, cause an increase in urethral pressure (Caine *et al.*, 1975; Awad and Downie, 1977; Langer, 1981; Hieble *et al.*, 1985). In BPH, the dynamic component of the prostatic obstruction, which could be responsible for almost 50% of the urethral pressure in the prostatic zone (Furuya *et al.*, 1982), is probably due to sympathetic stimulation of the smooth muscle located in the bladder neck, the prostate and the prostatic capsule. Several clinical studies using alpha-1 blockers in symptomatic patients with BPH (Boreham *et al.*, 1977; Caine *et al.*, 1978; Perlberg and Caine, 1982; Hedlund *et al.*, 1983; Martorana *et al.*, 1984; Ramsay *et al.*, 1985; Iacovou and Dunn, 1987; Kirby *et al.*, 1987; Chapple *et al.*, 1990; Fabricius *et al.*, 1990; Kawabe *et al.*, 1990; Sertcelik *et al.*, 1990) have shown clinical improvement and increases in urinary flow rates.

Alfuzosin is a new potent alpha-1 adrenoceptor antagonist (Cavero and Hicks, 1985; Cavero *et al.*,

1985) with a marked effect on the lower urinary tract in animal studies. A long-term clinical trial involving 518 patients with BPH revealed a significant and long-lasting improvement in urinary symptoms in the alfuzosin-treated patients when compared with those receiving placebo (Jardin *et al.*, 1991). The aim of the present study was to investigate the onset of action of alfuzosin, using uroflowmetry, in symptomatic patients with BPH following a single oral dose.

Patients and Methods

This multicentre, double-blind, placebo-controlled, parallel group study was conducted in urology out-patient clinics at 8 French hospitals between October 1989 and July 1990. The study was authorised by the Ethical Committee of the co-ordinating centre (Hôpital St Louis) and written informed consent was obtained from all patients. Those suffering from BPH who fulfilled the inclusion criteria (Table 1) were given 3 placebo tablets per day for 7 days. At the end of this single-blind, placebo run-in period, urinary flow measurements were carried out (H0): if the peak flow rate (PFR) was less than 15 ml/s, patients were randomly allocated to a single tablet of alfuzosin 1.25 mg, alfuzosin 2.5 mg, or matching placebo. Urinary

Table 1 Selection Criteria

Male > 50 < 80 years old.
Benign prostatic hypertrophy (digital $\pm$ transrectal echographic examination).
$\geq$ 6-month duration of voiding symptoms.
Maximum flow rate < 15 ml/s with voided volume $\geq$ 150 ml.

flow measurements (peak flow rate, voided volume, voiding time and calculated mean flow rate) were performed 1 h 30 min after administration of the preparation (H1.30). Supine and erect blood pressure and heart rate were monitored before dosing (H0) and at H1.30. In addition, a blood sample to determine the plasma level of alfuzosin was collected at H1.30. All urinary flow measurements were carried out using the same device (Dantec Urolyn 1000). All of the flow rate curves were read on a blind basis by the study co-ordinator (P.T.) at the end of the study, for validation purposes. Increases in the peak and mean flow rates were considered the main criteria of efficacy.

According to a variance equal to 12 ml/s and a minimal benefit of 3 ml/s (versus placebo) in the mean PFR increase, 21 patients were to be included per treatment group in order to obtain α and β error risks equal to 5 and 20% respectively. Thus 90 patients were to be included in the study in order to obtain 60 evaluable patients. Patients were sequentially allocated to the treatment groups and randomisation was balanced within centres. All patients were included in the "intention to treat" analysis. All comparisons were carried out using a 2-tailed test with α equal to 5%. The following analyses

were performed: comparison of baseline distributions (H0) in order to test the homogeneity of the 3 treatment groups, and between-group comparison of the raw distributions and relative distributions, i.e. differences from H0. A 1-way analysis of variance (ANOVA) was used for ordinal parameters and a Pearson's (chi-squared) test for qualitative parameters. Pairwise comparisons were performed applying a multiple comparison *t* method. Corrected significance levels were calculated using the Bonferroni-Holm procedure. An additional analysis was carried out in patients with initial peak flow rates below 10 ml/s. An *a posteriori* analysis, irrespective of the dose of alfuzosin, i.e. with only 2 treatment groups, was also conducted.

Results

In all, 93 patients were randomised: 31 were assigned to placebo, 31 to alfuzosin 1.25 mg and 31 to alfuzosin 2.5 mg. Their ages ranged from 47 to 80 years (mean 64.6). At entry, the 3 groups did not differ significantly with respect to duration of symptoms, total symptom score and uroflowmetry parameters (Table 2). Mean age was slightly higher in the alfuzosin 1.25 mg group and residual urine more frequent in both alfuzosin groups. Seventeen patients suffered from hypertension (placebo: $n=3$; alfuzosin 1.25 mg: $n=6$; alfuzosin 2.5 mg: $n=8$). Two patients (placebo: $n=2$) had a PFR > 15 ml/s at H0, which constituted a major protocol deviation and 2 patients (alfuzosin 1.25 mg $n=1$; alfuzosin 2.5 mg $n=1$) had no detectable plasma level of alfuzosin: these patients were included in the "intent to treat" analysis.

Table 2 Clinical Characteristics

	Placebo ($n=31$) Mean (SEM)	Alfuzosin 1.25 mg ($n=31$) Mean (SEM)	Alfuzosin 2.5 mg ($n=31$) Mean (SEM)	P
Age (years)	62.0 (1.5)	65.3 (1.1)	66.4 (1.3)	0.04†
Duration of voiding symptoms (months)	18.4 (2.3)	22.2 (3.3)	25.0 (3.1)	0.27†
Total symptom score*	3.84 (0.24)	4.32 (0.28)	3.87 (0.26)	0.34†
Residual urine (no. of patients)	15	22	23	0.04‡
(ml)	72 (11)	101 (22)	87 (11)	0.51†
Peak flow rate (ml/s)				
D-7	9.54 (0.47)	9.47 (0.44)	9.85 (0.41)	
D0**	9.79 (0.67)	9.25 (0.48)	9.85 (0.50)	0.70†

*Total symptom score: sum of voiding symptoms (nocturia, daytime frequency, urgency, terminal dribbling, impairment of the quality of the stream, hesitancy, sensation of incomplete bladder emptying (0 = absent, 1 = present))

†ANOVA

‡Chi-squared test

**After 1 week's treatment with placebo.

After a single dose of alfuzosin, flow rates increased significantly when compared with placebo. Peak flow rates tended to increase in a dose-dependent manner (Table 3) (Fig. 1). The increase in PFR was significantly greater in the 62 patients who received alfuzosin ($+2.31 \pm 0.5$ ml/s, *i.e.* 28.7%) than in those from the placebo group (0.53 ± 0.5 ml/s, *i.e.* 7.5%). A dose-dependent increase in the mean flow rate was observed (Fig. 2) with a 0.44 ± 0.3 ml/s (18.6%) increase in the alfuzosin 1.25 mg group and a 1.25 ± 0.5 ml/s (38.5%) increase in the alfuzosin 2.5 mg group. A dose-effect relationship was also observed in the voided volume, but the voiding time was not significantly affected. In the 47 patients with an initial peak flow rate <10 ml/s (*i.e.* with the most severe obstruction), the mean increase in PFR was greater: the mean ($\pm$ SEM) absolute variation versus baseline was $+1.14 \pm 0.5$ ml/s ($+17\%$) in the placebo group, $+1.67 \pm 0.7$ ml/s ($+26\%$) in the alfuzosin 1.25 mg group and $+3.75 \pm 1.2$ ml/s ($+55\%$) in the alfuzosin 2.5 mg group (Table 4) (Fig. 3).

The mean variations in urinary flow parameters after 1 week's treatment with placebo were minimal (Table 2).

Alfuzosin was well tolerated, with only one adverse event reported in the alfuzosin 2.5 mg group (a moderate hypertensive reaction). However, asymptomatic postural hypotension was recorded in 5 patients in the alfuzosin 2.5 mg group, 2 patients in the alfuzosin 1.25 mg group and none in the placebo group.

Mean supine and erect systolic and diastolic blood pressure did not change significantly in the 3 groups. Heart rate was stable in the placebo and alfuzosin 1.25 mg group. An increase in heart rate was observed in patients who received alfuzosin 2.5 mg: supine HR from $75.2 \text{ bpm} \pm 1.9$ (H0) to $80.0 \text{ bpm} \pm 2.1$ (H1.30), erect HR from $80.6 \text{ bpm} \pm 2.0$ (H0) to $85.6 \text{ bpm} \pm 2.5$ (H1.30) (comparison between groups $P=0.035$ and 0.06 respectively). No concentration-effect relationship was observed.

Discussion

Alpha-blockers have been shown to alleviate voiding symptoms in BPH, increase flow rates and decrease the volume of residual urine during long-term administration (Boreham *et al.*, 1977; Caine

Table 3 Variations in Uroflowmetric Parameters following a Single Dose of Placebo or Alfuzosin 1.25 mg or 2.5 mg

	Placebo (<i>n</i> = 31) Mean (SEM)	Alfuzosin 1.25 mg (<i>n</i> = 31) Mean (SEM)	Alfuzosin 2.5 mg (<i>n</i> = 31) Mean (SEM)	Total alfuzosin (<i>n</i> = 62) Mean (SEM)
Peak flow rate (ml/s)				
Before (H0)	9.79 (0.67)	9.25 (0.48)	9.85 (0.50)	9.55 (0.35)
After (H1.30)	10.33 (0.84)	11.22 (0.83)	12.50 (0.84)	11.86 (0.59)
Absolute variation	$+0.53$ (0.5) ($+7.5\%$)	$+1.97$ (0.6) ($+23.1$)	$+2.65$ (0.8) ($+34.3$) $P0.08\uparrow$	$+2.31$ (0.5) ($+28.7$) $P0.041\uparrow$
Mean flow rate (ml/s)				
Before (H0)	4.88 (0.47)	4.44 (0.39)	4.33 (0.32)	4.39 (0.25)
After (H1.30)	4.52 (0.43)	4.88 (0.42)	5.58 (0.52)	5.23 (0.33)
Absolute variation	-0.37 (0.3) (-1.5%)*	$+0.44$ (0.3) ($+18.6$)	$+1.25$ (0.5) ($+38.5$) $P0.023\uparrow$	$+0.85$ (0.3) ($+28.6$) $P0.018\uparrow$
Voided volume (ml)				
Before (H0)	275 (18)	244 (15)	265 (23)	255 (14)
After (H1.30)	306 (22)	310 (23)	352 (27)	331 (18)
Absolute variation	$+31$ (18) ($+17.8\%$)*	$+66$ (23) ($+36.3$)	$+87$ (22) ($+45.6$) $P0.22\uparrow$	$+75$ (16) ($+41.0$) $P0.10\uparrow$
Voiding time (s)				
Before (H0)	69.7 (7.8)	64.2 (5.6)	70.2 (7.6)	67.2 (4.7)
After (H1.30)	88.5 (13.4)	75.1 (7.8)	82.0 (11.3)	78.6 (6.8)
Absolute variation	$+18.8$ (11.6) ($+38.5\%$)*	$+11.0$ (7.7) ($+31.8$)	$+11.8$ (7.9) ($+23.1$) $P0.75\uparrow$	$+11.4$ (5.5) ($+27.4$) $P0.53\uparrow$

* (%) relative variation

$\uparrow$ Treatment effect, ANOVA.

$\uparrow$ Comparison alfuzosin (1.25 mg + 2.5 mg) vs placebo.

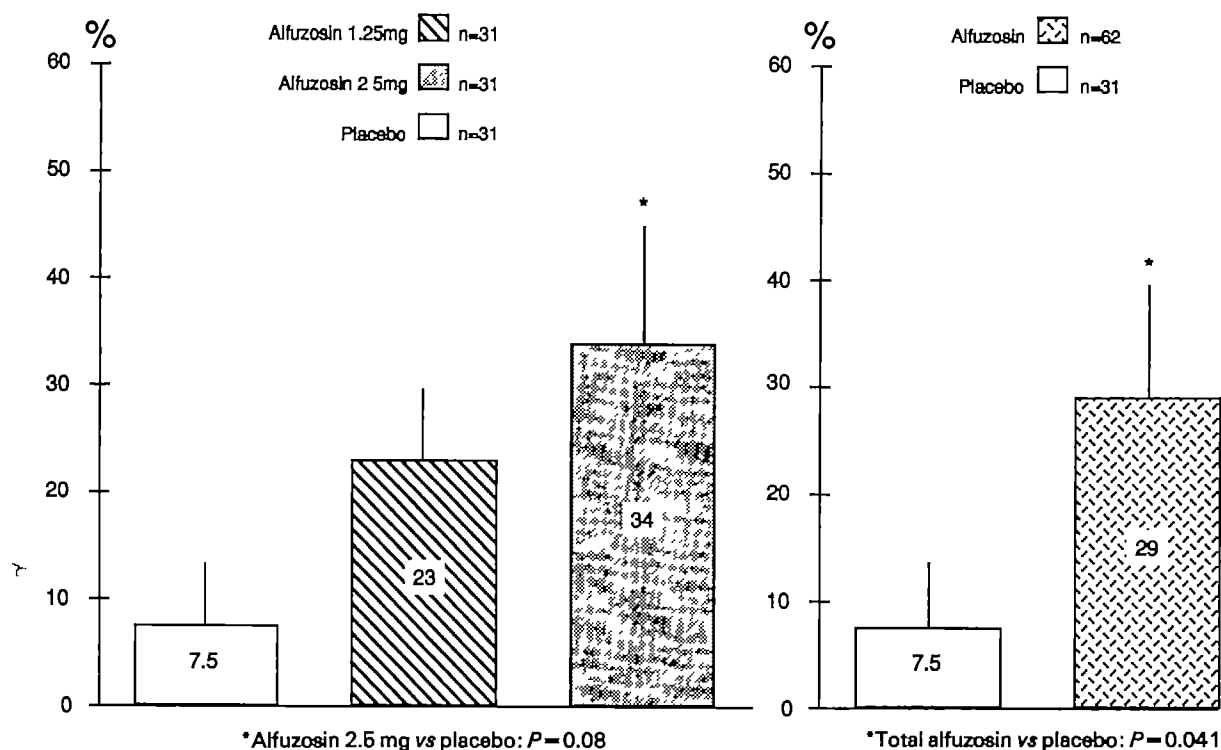


Fig. 1 Variations in peak flow rate following a single dose of alfuzosin 2.5 mg or 1.25 mg or placebo: mean (SEM) relative variations H1.30-H0.

et al., 1978; Hedlund *et al.*, 1983; Martorana *et al.*, 1984; Iacovou and Dunn, 1987; Kirby *et al.*, 1987; Chapple *et al.*, 1990; Fabricius *et al.*, 1990; Kawabe *et al.*, 1990; Sertcelik *et al.*, 1990), and for up to 6 months with alfuzosin (Jardin *et al.*, 1991). The relative increase in peak flow rate after treatment with alpha-1 blockers is approximately 30%.

This single-dose, double-blind, randomised, placebo-controlled study was conducted in order to document the onset of action of alfuzosin on urinary

flow parameters in patients with BPH. After a single oral dose, alfuzosin significantly increased flow rates 1 h 30 min after administration, in a dose-dependent manner. The increase in peak flow rate in the pooled alfuzosin (1.25 and 2.5 mg) group was statistically significant compared with the placebo group and was close to statistical significance when the alfuzosin 2.5 mg group was compared with the placebo group. Half of the patients initially had a PFR < 10 ml/s, an inclusion criteria

Table 4 Variations in Peak Flow Rates in Patients with an Initial Peak Flow Rate < 10 ml/s

	Peak flow rate			P*
	Placebo (n=14) Mean (SEM)	Alfuzosin 1.25 mg (n=17) Mean (SEM)	Alfuzosin 2.5 mg (n=16) Mean (SEM)	
Before (H0) (ml/s)	6.29 (0.49)	7.29 (0.38)	7.59 (0.38)	
After (H1.30) (ml/s)	7.43 (0.83)	8.96 (0.71)	11.34 (1.14)	
Absolute variation (ml/s)	+1.14 (0.54)	+1.67 (0.67)	+3.75 (1.2)	0.10
Relative variation (%)	+17.2 (9.9)	+26.1 (11.3)	54.9 (18.4)	0.15

*ANOVA; treatment effect

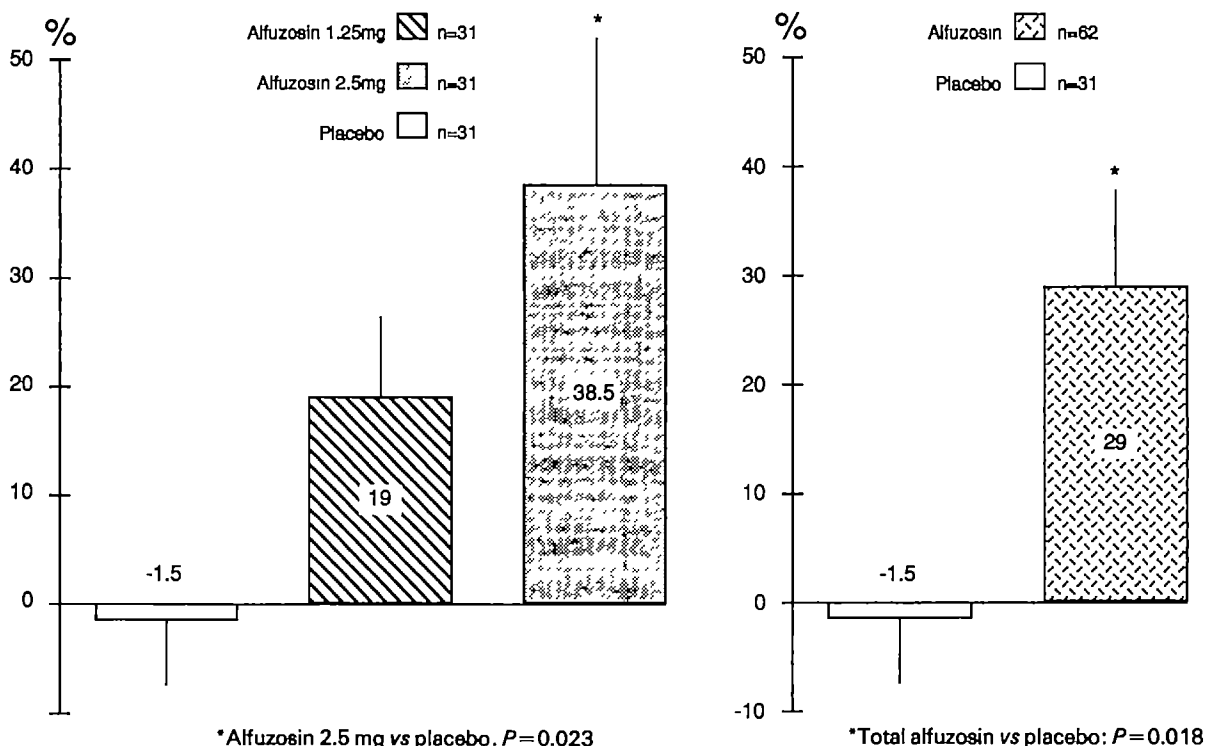


Fig. 2 Variations in mean flow rate following a single dose of alfuzosin 2.5 mg or 1.25 mg or placebo: mean (SEM) relative variations H1.30-H0.

recommended by the Food and Drug Administration (Boyarsky *et al.*, 1977) for BPH trials of alpha-1 blockers. In those obstructed patients who received alfuzosin 2.5 mg, the increase in PFR (+55%) was greater than in the total alfuzosin 2.5 mg group (+34%). A similar increase (+43%) in PFR was observed at the end of a 6-month placebo-controlled study in patients with an initial PFR <10 ml/s who were treated with alfuzosin 2.5 mg *t.i.d.* Thus alfuzosin 2.5 mg increases PFR from the first intake; this effect is maintained at a similar level during long-term therapy and is of a similar magnitude to that of other alpha-1 blockers. Moreover, the design of this study, aimed at evaluating the effect of a single oral dose on urinary flow parameters, could be useful in assessing alpha-1 blockers in BPH.

Alfuzosin produced a significant increase in mean flow rates (MFR) following a single oral dose and also during long-term administration (Jardin *et al.*, 1991); this was associated with an improvement in voided volume, probably the result of an increase in volume producing a strong desire to void, as observed in a urodynamic study by Ramsay

et al. (1985). MFR was also the most sensitive uroflowmetric parameter in a recent 1-month study with a new alpha-1 blocker YM617 (Kawabe *et al.*, 1990). This finding could suggest that the improvement in voiding symptoms seen with some alpha-1 blockers could be partly due to an increase in bladder capacity and compliance, in addition to a decrease in urethral pressure. There is evidence to support the claim that the normal β -type response of the detrusor to adrenergic stimulation is transformed, in some cases of BPH, to an α contractile response, resulting in detrusor muscle contraction and irritative symptoms (Rohner *et al.*, 1978; Perlberg and Caine, 1982; Caine, 1986). The bladder response to α blockade could also account for the decrease in residual urine observed in some alpha-1 blocker trials (Hedlund *et al.*, 1983; Kawabe *et al.*, 1990).

Urinary flow parameters are known to have an appreciable intra-individual variability (Drach *et al.*, 1979; Karl *et al.*, 1986). However, in patients who received placebo in this study, only minor variations in PFR were observed according to the change in mean values.

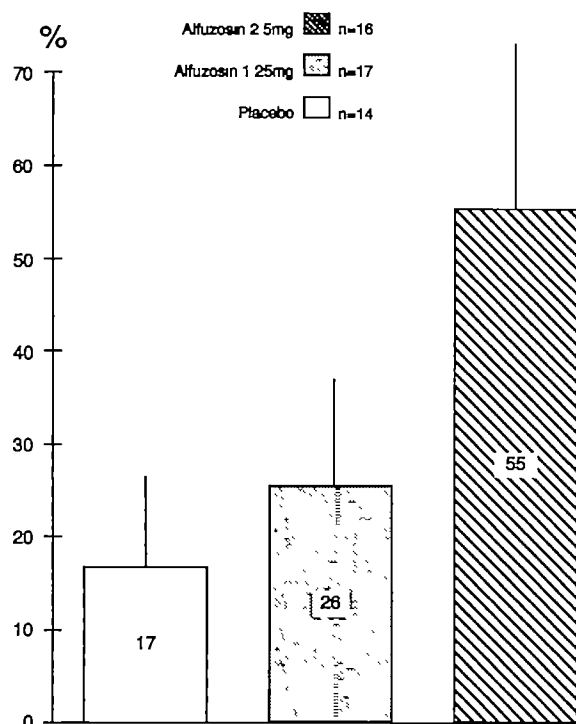


Fig. 3 Increase in peak flow rate in 47 patients with initial PFR < 10 ml/s: mean (SEM) relative variations H1.30–H0.

In animals, intravenous administration of alfuzosin preferentially blocks α -1 adrenoceptors of the lower urinary tract rather than those of vascular smooth muscle (personal communication). This might explain the mild variations in vital signs observed in this study, where cardiovascular parameters were carefully monitored.

In conclusion, alfuzosin, a new α -1 blocker, increased flow rates in patients with BPH shortly after administration of a single oral dose, in a dose-related manner. Only minor changes were observed following a single dose of placebo. The safety of the first dose of alfuzosin is confirmed.

Acknowledgements

This work was supported in part by Synthelabo Recherche. The authors are most grateful to C. Laude for her technical assistance. The DUALF Group included the following. J. Petit (Amiens), C. Coulange (Marseille), M. Tenaillon (Albi), D. Rossi (Marseille), H. Navratil (Nîmes), O. Haillot (Tours), P. Teillac (Paris), P. Coloby (Pontoise) and A. Le Duc (Paris).

References

Awad, S. A. and Downie, J. W. (1977). The adrenergic component in the proximal urethra. *Urol. Int.*, **32**, 192–197.

- Boreham, P. F., Braithwaite, P., Milewski, P. *et al.* (1977). Alpha-adrenergic blockers in prostatism. *Br. J. Surg.*, **64**, 756–757.
- Boyarsky, S., Jones, G., Paulson, D. F. *et al.* (1977). A new look at bladder neck obstruction by the Food and Drug Administration Regulators: guidelines for investigation of benign prostatic hypertrophy. *Trans. Am. Assoc. Genito-Urin. Surg.*, **68**, 29–32.
- Caine, M. (1986). The present role of alpha-adrenergic blockers in the treatment of benign prostatic hypertrophy. *J. Urol.*, **136**, 1–4.
- Caine, M., Perlberg, S. and Meretyk, S. (1978). A placebo-controlled double-blind study of the effect of phenoxybenzamine in benign prostatic obstruction. *Br. J. Urol.*, **50**, 551–554.
- Caine, M., Raz, S. and Zeigler, M. (1975). Adrenergic and cholinergic receptors in the human prostate, prostatic capsule and bladder neck. *Br. J. Urol.*, **47**, 193–202.
- Cavero, I. and Hicks, P. E. (1985). Effects of alfuzosin and idazoxan on nerve mediated contractions in the rabbit isolated urethra (Abstract). *Br. J. Pharmacol.*, **86**, 612 P.
- Cavero, I., Hicks, P. E. and Lefèvre-Borg, F. (1985). α -adrenoceptor antagonist effects of alfuzosin in rabbit and dog lower urinary tract. (Abstract). *Br. J. Pharmacol.*, **86**, 416 P.
- Chapple, C. R., Christmas, T. J. and Milroy, E. J. G. (1990). A twelve-week placebo-controlled study of prazosin in the treatment of prostatic obstruction. *Urol. Int.*, **45**, 47–55.
- Drach, G. W., Layton, T. N. and Binard, W. J. (1979). Male peak urinary flow rate: relationship to volume voided and age. *J. Urol.*, **122**, 210–214.
- Fabricius, P. G., Weizert, P., Duzendorfer, V. *et al.* (1990). Efficacy of once-a-day terazosin in benign prostatic hyperplasia: a randomized, double-blind, placebo controlled clinical trial. *The Prostate (Suppl. 3)*, 85–93.
- Furuya, S., Kumamoto, Y., Yomoyama, E. *et al.* (1982). Alpha adrenergic activity and urethral pressure in prostatic zone in benign prostatic hypertrophy. *J. Urol.*, **128**, 836–839.
- Hedlund, H., Anderson, K. E. and Ek, A. (1983). Effects of prazosin in patients with benign prostatic obstruction. *J. Urol.*, **130**, 275–278.
- Hieble, J. P., Caine, M. and Zalaznik, E. (1985). *In vitro* characterization of the α -adrenoceptors in human prostate. *Eur. J. Pharmacol.*, **107**, 111–117.
- Iacovou, J. W. and Dunn, M. (1987). Indoramin—an effective new drug in the management of bladder outflow obstruction. *Br. J. Urol.*, **60**, 526–528.
- Jardin, A., Bensadoun, H., Delauche-Cavallier, M. C. *et al.* (1991). Alfuzosin for treatment of benign prostatic hypertrophy. *Lancet*, **337**, 1457–1461.
- Karl, C., Gerlach, R., Hannapel, J. *et al.* (1986). Uroflow measurements: their information yield in a long-term investigation of pre and post operative measurements. *Urol. Int.*, **41**, 270–275.
- Kawabe, K., Veno, A., Aso, Y. *et al.* (1990). Use of an α -blocker, YM617, in the treatment of benign prostatic hypertrophy. *J. Urol.*, **144**, 908–912.
- Kirby, R. S., Coppinger, S. W. C., Corcoran, M. O. *et al.* (1987). Prazosin in the treatment of prostatic obstruction. A placebo-controlled study. *Br. J. Urol.*, **60**, 136–142.
- Langer, S. Z. (1981). Presynaptic regulation of the release of the catecholamines. *Pharmacol. Rev.*, **32**, 337–362.
- Martorana, G., Gliberti, C., Damonte, P. *et al.* (1984). The effect of prazosin in benign prostatic hypertrophy, a placebo-controlled double-blind study. *IRCS Med. Sci.*, **12**, 11–12.
- Perlberg, S. and Caine, M. (1982). Adrenergic response of bladder muscle in prostatic obstruction. *Urology*, **20**, 524–527.

- Ramsay, J. W. A., Scott, G. I. and Whitfield, H. N. (1985). A double-blind controlled trial of a new α -1 blocking drug in the treatment of bladder outflow obstruction. *Br. J. Urol.*, **57**, 657-659.
- Robner, T. J., Hannigan, J. D. and Sanford, E. J. (1987). Altered *in vitro* adrenergic responses of drug detrusor muscle after chronic bladder outlet obstruction. *Urology*, **11**, 357-361.
- Sertcelik, M. N., Ünal, S., Özgür, S. *et al.* (1990). Prazosin, a selective alpha 1 receptor blocker in the treatment of benign prostatic hypertrophy. *Curr. Therap. Res.*, **48**, 1066-1074

The Authors

- P. Teillac, MD, Professor, Hôpital St Louis.
M. C. Delauche-Cavallier, MD, Research Fellow, Synthélabo Recherche.
P. Attal, MD, Research Fellow, Synthélabo Recherche.

Requests for reprints to: M. C. Delauche-Cavallier, Synthélabo Recherche L.E.R.S., B.P. 110-31 avenue Paul Vaillant-Couturier, 92225 Bagneux CEDEX, France.

Finasteride in the Treatment of Benign Prostatic Hyperplasia. A Urodynamic Evaluation

R. S. KIRBY, JENNY BRYAN, I. EARDLEY, T. J. CHRISTMAS, S. LIU, S. A. V. HOLMES, J. A. VALE, K. SHANMUGANATHAN and JUDITH A. WEBB

Departments of Urology and Radiology, St Bartholomew's Hospital, London

Summary—A group of 69 men with bladder outflow obstruction due to benign prostatic hyperplasia (BPH) were treated in a double-blind, placebo-controlled study with finasteride (Proscar, MK-906), a 5- α reductase inhibitor, 5 mg or 10 mg/day or placebo for 3 months; subsequently, 20 patients received finasteride 5 mg/day for a further 9 months in an open extension study. In treated patients dihydrotestosterone declined by over 60%, remaining unchanged with placebo. Symptom scores fell significantly in all 3 groups. Mean maximum flow rates fell slightly in placebo-treated patients but improved by 1.5 ml/s in the 10 mg group and by 3.3 ml/s in the 5 mg group. After 1 year's treatment, the reduction in symptom score and increase in flow rate were well maintained; the mean prostate volume was reduced by 14% and prostatic specific antigen declined by 28%. It was concluded that finasteride shows some efficacy in the treatment of BPH, with minimal toxicity, but 12 months of therapy or longer may be necessary to achieve maximal effect.

Benign prostatic hyperplasia (BPH) afflicts the majority of men over the age of 60 and in a considerable proportion causes significant bladder outflow obstruction (Garraway *et al.*, 1991). Currently the mainstay of treatment is transurethral resection of the obstructing prostatic tissue (TURP) and more than 500,000 of these operations were performed worldwide last year. Although this is generally a safe and effective procedure, there is little doubt that the development of a pharmacological agent which arrested or reversed the disease process, as opposed to simply affording symptomatic relief, would be a significant advance.

As early as 1786 John Hunter observed that the prostate was an androgen-dependent gland. At the turn of the last century Cabot (1886) performed bilateral orchiectomy for infravesical obstruction resulting from BPH in 79 patients and reported 80% success rates. However, the assessment of

response was totally subjective and it is not entirely clear whether some of the patients were in fact suffering from malignant rather than benign prostatic enlargement. Huggins and Stevens (1940) reported 3 cases of BPH treated by surgical castration; in 2 cases when the prostate was removed some months later there was both macroscopic and microscopic evidence of glandular atrophy. Following this, Peirson (1946) reported shrinkage of the prostate using stilboestrol therapy. Subsequently a number of small and often poorly controlled studies suggested that several drugs with anti-androgenic activity, including 17- α hydroxyprogesterone caproate (Geller *et al.*, 1965; Wolf and Madson, 1968), cyproterone acetate (Scott and Wade, 1969) and flutamide (Caine *et al.*, 1975; Stone *et al.*, 1989) might have some beneficial effect in BPH. Within the last few years both Bosch *et al.* (1989) and Peters and Walsh (1987) showed that medical castration using an LHRH analogue reduced prostatic volume by 30% with mild improvement in infravesical obstruction. However,

the clinical value of all of these forms of androgen deprivation therapy for BPH is inevitably limited by the induction of hypogonadism and associated loss of libido.

In 1963 Farnsworth and Brown observed that within the prostate testosterone undergoes metabolism to dihydrotestosterone (DHT). Shimazaki *et al.* (1965) later characterised the enzyme responsible and named it 5- α reductase, also showing it to require the reduced form of nicotinamide adenine dinucleotide (NADPH) for this activity. On the basis of experiments in rats, Bruchovsky and Wilson (1968) and Anderson and Liao (1968) suggested that DHT rather than testosterone was the main androgen modulating prostate growth. The pivotal role of DHT in inducing and maintaining prostate growth was subsequently confirmed by the studies of Imperato-McGinley *et al.* (1974), who investigated 12 families with 24 men suffering from congenital 5- α reductase deficiency and consequently low DHT levels. The females in these families were apparently unaffected, but the males who masculinised after puberty were observed to have normal libido but only rudimentary prostate development and never developed prostatic enlargement or BPH.

Finasteride is an orally active neutral 4-azasteroid that competitively inhibits 5- α reductase (Fig. 1), producing a profound fall in serum and intraprostatic DHT levels without lowering testosterone levels (Geller, 1990; Stoner, 1990). Finasteride itself possesses no androgenic, anti-androgenic or steroid hormone-related properties. Preliminary clinical studies indicate that treatment continued for 6 months causes a reduction in prostate volume of about 28% in BPH patients (Stoner, 1990). In these studies clinically significant adverse events were not seen and no important changes in other

Table 1 Total Symptom Score

Obstructive	Irritative
Impairment of force of stream	Urgency of micturition
Hesitancy of micturition	Dysuria
Sensation of incomplete emptying	Urge incontinence (clothes wet)
Intermittent stream	Difficulty initiating urinary flow
Terminal dribbling	

(Each symptom scored from 0–5).

hormone parameters were observed. The aim of this study was to assess urodynamically the potential role of this compound in the treatment of patients with infravesical obstruction resulting from established BPH.

Patients and Methods

The study group comprised 69 men of mean age 64.4 years (range 48–87) presenting with bladder outflow obstruction due to BPH. Ethics Committee permission for the investigation had previously been granted and written informed consent was obtained in every case. At baseline all patients underwent symptom evaluation using a scoring system modified from Boyarsky *et al.* (1977) (Table 1), as well as clinical examination and serology, including prostate specific antigen (PSA), testosterone, DHT, luteinising hormone (LH) and follicle stimulating hormone (FSH) levels. Only those patients with objective evidence of obstruction (*i.e.* raised maximum subtracted detrusor pressure during voiding (> 50 cm H₂O) and reduced maximum urinary flow rate (< 15 ml/s) on pressure-flow urodynamics with subtraction of intra-abdominal pressure and repeated uroflowmetry with voided volumes > 150 ml) were entered into the study. Each patient also underwent transrectal ultrasonography (TRUS) by one of 2 experienced radiologists (J.A.W. or K.S.) using an ATL Ultramark 5 ultrasound machine with a 7.5 MHz biplanar probe, when a careful record of prostate volume was obtained by measurement of maximum gland dimensions in the axial, sagittal and coronal planes. The following formula was then used to calculate the volume of the prostate gland:

$$\text{Volume} = 4/3\pi (\text{axial}/2) \times (\text{coronal}/2) \times (\text{sagittal}/2)$$

After a 1-week placebo run-in period the patients were randomised to either finasteride 5 mg/day,

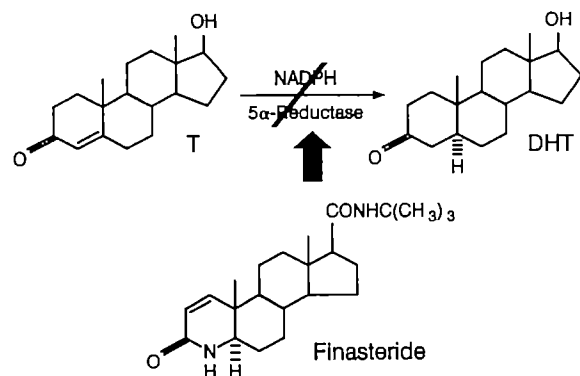


Fig. 1 Mechanism of action of finasteride.

finasteride 10 mg/day or identical placebo for 3 months. Patients were seen at monthly intervals for assessment of the symptom score and evaluation of adverse effects; uroflow determinations and blood tests were also repeated at monthly intervals. At the end of the 3-month, double-blind study period patients underwent a second pressure/flow urodynamic evaluation, as well as TRUS to determine prostate volume. Subsequently each individual was offered the opportunity of continuing finasteride at 5 mg/day on an open protocol basis with monthly symptom scoring, PSA determination at 6 and 12 months and prostate volume measurement by TRUS at 1 year. Alternatively, the patient could elect to undergo routine TURP.

The efficacy analyses for the double-blind period were performed by using the all-patients-treated approach, including all patients with voiding measurements at both baseline and under treatment. Dropouts were included by carrying forward the last observation on treatment of timepoints subsequent to dropout.

For the extension study, end points analyses were performed and data were not carried forward. All within group tests were made by using the Wilcoxon signed Rank test.

Covariance analyses were used to compare the treatment groups with respect to the ranked values of change (or % change) from baseline with the ranks of the baseline measurements as covariate.

Results

Of the 69 patients entering the study there were 12 withdrawals, 4 for adverse events and 8 for various unrelated reasons. However, all patients were included in the analysis as mentioned previously.

Mean DHT, testosterone and PSA levels, and prostate volumes at baseline and at 3 months are shown in Table 2, while corresponding symptom scores and urodynamic parameters are shown in Table 3. Serum DHT levels remained unchanged in the placebo-treated group but showed significant declines of 72.4% in the 10 mg group and 61.4% in the 5 mg group ($P < 0.001$) (Fig. 2). These changes were accompanied by a mild elevation within the normal range of LH and testosterone levels; FSH levels remained unchanged. PSA levels declined by a mean of 6.2% in placebo-treated patients but by 19.9% in the 10 mg group and by 20.5% ($P < 0.01$) in the 5 mg group.

Prostate volume measurements showed small non-significant reductions in all 3 groups over the

3-month study. The larger mean prostate sizes in the placebo group at baseline were the result of inclusion through randomisation of several patients with particularly large glands in this group.

Symptom scores fell significantly in all 3 groups after 3 months' treatment ($P < 0.05$). Maximum urinary flow rates deteriorated slightly (-1.1 ml/s) in the placebo-treated patients during the study but increased by 1.5 ml/s in the 10 mg group and by 3.3 ml/s in the 5 mg group, the latter increase reaching statistical significance ($P < 0.001$). These improvements in flow rates cannot simply be accounted for by increased voided volumes, for these did not change significantly during the study period.

Maximum subtracted detrusor pressures during voiding increased slightly in the placebo group and decreased by 22.3 cm H₂O in the 10 mg group and by 6.1 cm H₂O in the 5 mg group, although not to a statistically significant degree. Residual urine volumes fell in all groups, again not significantly.

In the 1-year open extension study with finasteride 5 mg (Tables 4 and 5), prostate volumes decreased by a mean of 14.1% ($P < 0.01$); this was accompanied by a continued decline in PSA levels, with mean reductions of 22.7% at 6 months ($P < 0.005$) and 28% at 12 months ($P < 0.005$) (Fig. 3). Improvements in symptom scores were well maintained; a decrease of 5.4 (32%) ($P < 0.001$) in score was seen at 12 months, and the mean maximum uroflow value increased over 1 year from 9.6 to 12.3 ml/s ($+2.7$ ml/s, $+28\%$) ($P < 0.001$). Patients who switched to finasteride 5 mg from placebo at the end of the double-blind study showed an improvement in maximum urinary flow rate over the subsequent 9 months (Fig. 4).

Adverse events during both the double-blind and open continuation study were minor and few. Four patients discontinued treatment because of adverse events. Two patients, one on placebo and one taking finasteride 5 mg/day, developed acute urinary retention; both successfully voided after TURP. One patient developed a mild skin rash while taking finasteride 10 mg/day; this was possibly drug-related and treatment was discontinued. Another patient on finasteride 5 mg developed a chest infection and withdrew. One further patient noticed a skin rash in the open extension study which disappeared spontaneously but recurred after cessation of the medication; this was probably unrelated to the drug. One patient developed erectile impotence while on finasteride 5 mg/day, but stayed in the 3-month study; on completing the trial and stopping the drug his potency returned. A

Table 2 Double-blind Period

Parameter	Placebo				5mg				10mg			
	Baseline		3-month		Baseline		3-month		Baseline		3-month	
	N	Mean % change (SD)	N	Mean % change (SD)	N	Mean % change (SD)	N	Mean % change (SD)	N	Mean % change (SD)	N	Mean % change (SD)
DHT (mmol/l)	21	1.8	1.7	-0.2 (48.6)	29	1.7	0.5	-61.4* (65.6)	16	2.7	0.7	-72.4* (14.0)
Testosterone (nmol/l)	21	16.9	17.0	1.7 (15.0)	30	17.9	18.5	10.3 (31.8)	16	18.1	22.4	-25.2* (27.7)
PSA (μ g/l)	14	5.0	4.0	-6.2 (28.3)	20	4.1	3.0	-20.5* (23.2)	5	3.0	2.2	-19.9 (26.1)
Prostate volume (ml)	10	54.3	52.1	-1.8 (14.4)	25	49.7	47.4	-2.5 (27.0)	3	37.7	35.7	-3.7 (11.9)

* $P < 0.01$

Table 3 Double-blind Period

Parameter	Placebo				5mg				10mg			
	Baseline		3-month		Baseline		3-month		Baseline		3-month	
	N	Mean change (SD)	N	Mean change (SD)	N	Mean change (SD)	N	Mean change (SD)	N	Mean change (SD)	N	Mean change (SD)
Symptom score	21	18.8	15.3	-3.5* (4.7)	31	19.3	15.3	-4.0* (5.5)	16	16.9	14.6	-2.3† (4.6)
Maximum flow rate (ml/s)	20	11.1	10.0	-1.1 (4.3)	32	7.2	10.5	3.3* (3.0)	15	9.3	10.8	1.5 (5.3)
Voided volume (ml)	20	217.9	226.8	8.9 (77.4)	32	205.2	235.8	30.6 (80.1)	15	234.9	251.8	16.9 (99.8)
Maximum voiding pressure (cmH ₂ O)	11	65.9	70.4	4.5 (36.4)	14	76.3	70.2	-6.1 (36.4)	14	68.3	46.0	-22.3 (53.1)
Residual urine (ml)	11	151.9	78.6	-73.4 (36.4)	23	104.2	87.5	-16.7 (36.4)	15	161.2	112.8	-48.4 (107.7)

* $P < 0.01$.† $P < 0.05$.

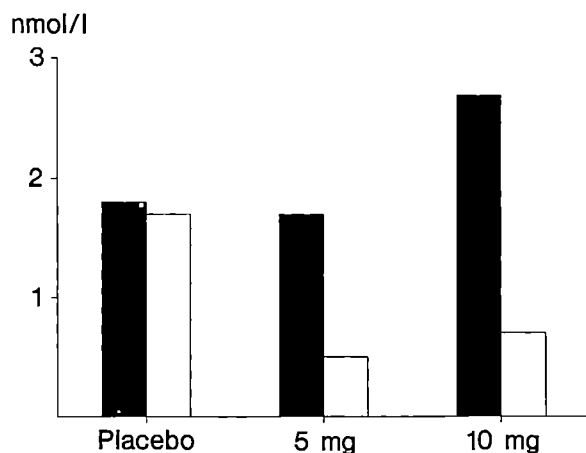


Fig. 2 Baseline and 3 month DHT levels in finasteride and placebo-treated groups.

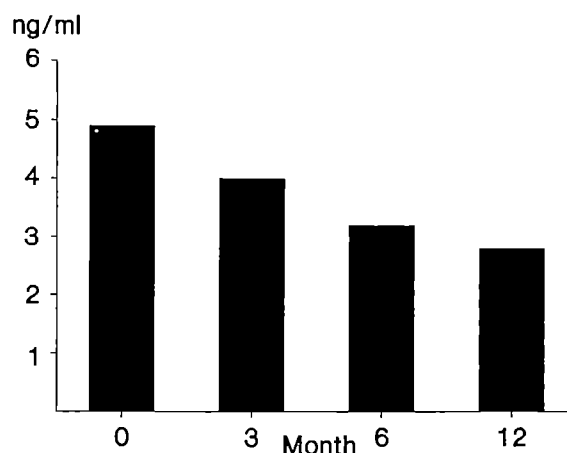


Fig. 3 Reduction in serum PSA over 1 year in patients treated with finasteride 5 mg/day.

Table 4 Extension

Parameter	N	Baseline	Month 12	Mean % change (SD)
Prostate volume (ml)	16	53.5	41.0	-14.1* (36.4)
PSA (µg/l)	16	4.9	2.8	-28.0* (30.0)

* $P < 0.01$.

Table 5 Extension

Parameter	N	Baseline	Month 12	Mean Change (SD)
Symptom score	16	20.1	13.7	-6.4* (6.3)
Maximum flow rate (ml/s)	16	9.6	12.3	-2.7* (2.7)
Voided Volume (ml)	16	226.8	240.9	14.1 (109.7)

* $P < 0.01$.

further patient complained of difficulty in achieving and maintaining erections during the open extension study, and again potency returned on cessation of the medication.

Discussion

Although infravesical obstruction resulting from BPH is nowadays seldom a cause of mortality, its

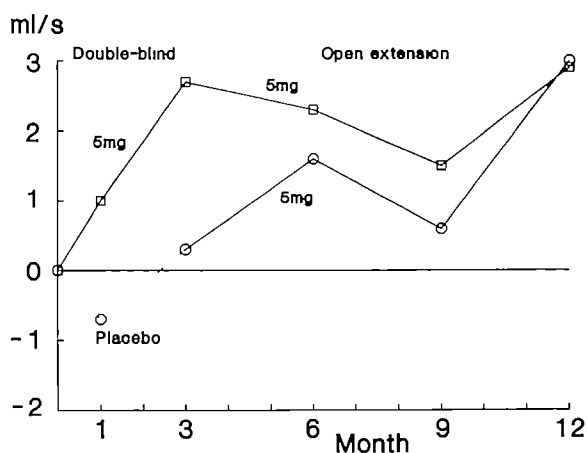


Fig. 4 Mean maximum flow rate changes in patients treated for 1 year, showing increasing flow rates in patients switched from placebo to finasteride 5 mg at 3 months.

almost ubiquitous presence in elderly men makes it an important source of morbidity. Moreover, with the pronounced demographic shift towards increasing longevity in developed and under-developed countries the economic burden of this disease seems certain to increase.

While the results of this pilot study do not unequivocally confirm the urodynamic efficacy of finasteride in relieving infravesical outflow obstruction due to BPH after 3 months' treatment, they do demonstrate that the drug has some beneficial activity in this very common disorder of elderly men.

The almost identical degree of suppression of serum DHT with both 5 and 10 mg dosages of

finasteride suggests that the lower dosage may be as effective as the 10 mg regime, and there were no important differences between the two in terms of either clinical efficacy or side effects, although the small numbers of patients in this study may have made it difficult to detect small differences. The improvement in symptom score seen in the placebo group highlights the importance of placebo effect on symptoms of prostatic obstruction, as has been noted in other studies involving drug therapy for BPH (Kirby *et al.*, 1987; Jardin *et al.*, 1991). However, the symptom score in those patients treated with finasteride in the double-blind study was well maintained up to 12 months in the open extension study. Parallel with this improvement in symptomatology observed in the finasteride-treated patients there was a small but measurable increase in maximum urinary flow as well as a trend towards reduced maximum subtracted intravesicular pressure during micturition; the fact that not all of these parameters achieved statistical significance probably reflects the relatively small size of the study group and the limited 3-month duration of treatment. The continuing PSA decline (-42%) observed at 1 year suggests that this drug may not reach maximal effect for many months or even years and indicates the need for longer-term controlled studies. In the present study, changes in prostate volume became apparent only after 3 months and during the open extension study, when the scans were admittedly open to observer bias. However, it must be borne in mind that there is at least a 10% margin of error in the measurement of prostate volume by transrectal ultrasound (Resnick, 1990) and it seems probable that, had magnetic resonance imaging been used as an imaging modality with its lower coefficient of variation in prostate volume measurement, some reduction in prostate size in those patients taking finasteride would have been apparent at 3 months. This was certainly the case in previously reported phase II studies with this compound (Gormley and Stoner, 1991).

The pathogenesis of BPH is still incompletely understood, but 2 factors—ageing and the presence of androgens—are known to be prerequisites for its development. The original observations of Siiteri and Wilson (1970)—that BPH tissue contains excess quantities of DHT—have subsequently been contested by Walsh *et al.* (1983). However, current research suggests that increased numbers of androgen receptors may be present in BPH tissue and that their modulation by DHT may result in the development of stromal and epithelial hyperplasia

within the prostate (Barrack *et al.*, 1983). BPH is a pathological process which develops in the transition and periurethral zone of the prostate and compresses the urethra, thereby increasing voiding pressures and reducing urinary flow. BPH tissue consists of 2 major components: fibromuscular stroma and glandular epithelium in varying proportions (Bartsch *et al.*, 1979) and there is evidence to suggest that it is predominantly the latter which requires androgens, and in particular DHT, to maintain its integrity (Walsh *et al.*, 1983). Since the prostate in different individuals may vary markedly in the relative proportions of stroma to epithelium (Price *et al.*, 1990), it seems possible that those glands with the highest ratio of epithelium to stroma may be those which respond maximally in terms of shrinkage to 5- α reductase inhibition. This might account for the observation that not all patients treated with finasteride appear to respond in terms of either flow rate improvement or prostate shrinkage.

The magnitude of the flow rate improvement seen in this study (mean 2.7 ml/s) (28%) is admittedly modest when compared with that of transurethral surgery, where flow rate improvements of more than 100% are not uncommon (Abrams, 1978). However, it must be remembered that the mean decline in maximum urinary flow associated with ageing, presumably as a result of developing BPH, is 0.2 ml/year (Drach *et al.*, 1979); thus 1 year's treatment with finasteride may be seen to achieve a reversal of more than 10 years' progressive uroflow decline with age. Although the mean maximum subtracted detrusor pressures during voiding in treated patients and controls were only about 70 cm of water (a value comparable to that recorded in a similar group of BPH sufferers treated with prazosin (Kirby *et al.*, 1987)), many subjects were urodynamically and symptomatically in the severely obstructed category, as witnessed by the observation that 2 individuals developed acute urinary retention during the trial. It does seem possible, therefore, that treatment of patients with this agent at an earlier stage of the disease might arrest its progression or even reverse the disorder, and thereby reduce the need for transurethral surgery, with its small but appreciable morbidity, mortality and reoperation rates (Roos *et al.*, 1989) and also provide a treatment option for those patients not considered candidates for surgery. However, a much larger study of considerably longer duration would be necessary to confirm this.

Perhaps a more realistic comparison might be drawn between treatment of BPH with finasteride

and treatment with an alpha-blocking agent, a number of which have been shown to have some efficacy in this condition (Kirby *et al.*, 1987; Jardin *et al.*, 1991). The mean peak and average flow rate improvements with these agents are in the order of 30%, but this is achieved at the expense of a small but significant incidence of postural hypotension, nasal stuffiness and tiredness. Moreover, there is some evidence to suggest some diminution of efficacy with time (Jardin *et al.*, 1991), perhaps due to tachyphylaxis or as a result of continuing prostatic enlargement. Since finasteride appears to act predominantly on the glandular component of BPH, and alpha blockers act to relax the smooth muscle component of fibromuscular stroma, the possibility exists that combining these therapies may achieve both rapid symptomatic relief and longer-term reversal of the underlying pathophysiological process of BPH.

One legitimate cause for concern in patients suffering from BPH treated long-term either with a 5-alpha reductase inhibitor, or indeed with an alpha blocker, is that a proportion of them might be harbouring undetected foci of carcinoma of the prostate. Between 10 and 20% of those patients who undergo TURP for what is assumed to be benign disease are subsequently found to harbour microscopic foci of malignancy. However, the observation that in BPH finasteride produces a progressive decline in PSA—a sensitive marker for carcinoma of the prostate—is somewhat reassuring. Moreover, phase II studies of finasteride in patients with metastatic carcinoma of the prostate have shown a mildly beneficial rather than deleterious clinical and biochemical effect (Fair *et al.*, 1991). However, more work needs to be done to clarify this issue. In cases of doubt, or where PSA is above 4 ng/ml (Hybritech Assay) (as was the case in a patient in our study who was subsequently found to have carcinoma of the prostate), multiple ultrasound-guided transrectal or transperineal prostatic biopsies should be obtained to exclude carcinoma before embarking on long-term medical therapy, and the patients should be carefully monitored during follow-up.

In conclusion, the results of this small study suggest that a proportion of patients who suffer infravesical obstruction resulting from BPH may respond with some prostatic shrinkage and a modest improvement in symptoms and urinary flow rates after long-term therapy with the 5-alpha reductase inhibitor finasteride. Although in these patients there was no clear correlation between symptomatic response and urodynamic response in prostate

volume, it seems possible that this might have been evident in a longer study. It is clear that therapy may have to be administered for at least 1 year before the maximum effect is obtained and consequently the onset of symptom relief will be gradual. More work is required before it can be predicted clinically which patients will respond best to this therapy and how long treatment should be administered before maximal effect is achieved. However, it does appear that finasteride, with its extremely low toxicity, may provide, for the first time, an acceptable medical therapy which is, in at least a proportion of patients, capable of arresting or reversing the pathogenesis of this most prevalent disorder of elderly men.

Acknowledgements

We thank Dr Elizabeth Stoner of Merck Sharp and Dohme Research Laboratories for the supply of finasteride 5 mg and 10 mg and matched placebo, and for financial support for the study. We also thank Messrs H. N. Whitfield and W. F. Hendry for allowing us to study patients in their care.

References

- Abrams, P. H. (1978). Urodynamic changes following prostatectomy. *Urol. Int.*, **33**, 181–186.
- Anderson, K. M. and Liao, S. (1968). Selective retention of dihydrotestosterone by prostatic nuclei. *Nature*, **219**, 227–229.
- Barrack, E. R., Bujnovsky, P. and Walsh, P. C. (1983). Subcellular distribution of androgen receptors in human normal benign hyperplastic and malignant prostatic tissues: characterisation of nuclear salt-resistant receptors. *Cancer Res*, **43**, 1107–1116.
- Bartsch, G., Muller, H. R., Oberholzer, M. *et al.* (1979). Light microscopic stereological analysis of the normal human prostate and of benign prostatic hyperplasia. *J. Urol.*, **122**, 487–491.
- Bosch, R. J., Griffiths, D. J., Blom, J. *et al.* (1989). Treatment of benign prostatic hyperplasia by androgen deprivation: effects on prostate size and urodynamic parameters. *J. Urol.*, **141**, 68–72.
- Boyarsky, S., Jones, G., Paulson, D. F. *et al.* (1977). A new look at bladder neck obstruction by the Food and Drug Regulators: guidelines for the investigation of benign prostatic hypertrophy. *Trans Am Assoc. Genito-Urin Surg*, **68**, 29–32.
- Bruchovsky, N. and Wilson, J. D. (1968). The conversion of testosterone to 5-alpha-Androstan-17beta-ol-3-one by rat prostate *in vivo* and *in vitro*. *J. Biol. Chem*, **243**, 2012–2021.
- Cabot, A. T. (1986). The question of castration for the enlarged prostate. *Ann. Surg.*, **24**, 265–301.
- Caine, M., Perlberg, S. and Gordon, R. (1975). The treatment of benign prostatic hypertrophy with flutamide: a placebo controlled study. *J. Urol.*, **114**, 564–568.
- Drach, G. W., Layton, T. N. and Binard, W. J. (1979). Male peak urinary flow rate: relationships to volume voided and age. *J. Urol.*, **122**, 210–214.
- Fair, W. R., Presti, J. C., Sogani, P. *et al.* (1991). Multicenter, randomized, double-blind placebo controlled study to investigate the effect of finasteride (MK-906) on Stage D prostate cancer. *J. Urol.*, **122**, 317A.

- Farnsworth, W. E. and Brown, J. R. (1963). Testosterone metabolism in the prostate. *Natl. Cancer Inst. Monogr.*, **12**, 323-325.
- Garraway, W. M., Collins, G. N. and Lee, R. J. (1991). High prevalence of benign prostatic hypertrophy in the community. *Lancet*, **338**, 469-471.
- Geller, J. (1990). Effect of Finasteride, a 5-alpha reductase inhibitor on prostate tissue androgens and prostate specific antigen. *J. Clin. Endocrinol. Metab.*, **71**, 1552-1555.
- Geller, J., Bora, R., Roberts, R. *et al.* (1965). The treatment of benign prostatic hypertrophy with hydroxyprogesterone caproate. Effect on clinical symptoms, morphology and endocrine function. *J.A.M.A.*, **193**, 121-128.
- Gormley, G. J. and Stoner, E. (1991). The role of 5 alpha reductase inhibitors in the treatment of benign prostatic hyperplasia. In *Problems in Urology; Controversies and Advances in the Treatment of Benign Prostatic Hyperplasia*. Volume 5 No. 3, pp. 436-440. Philadelphia: Lippincott.
- Huggins, C. and Stevens, R. A. (1940) The effect of castration on benign prostatic hypertrophy of the prostate in man. *J. Urol.*, **43**, 705-714.
- Hunter, J. (1786). *Observations on Certain Parts of the Animal Oeconomy* Bibliotheca Oesteriana, 38-39p, published in London.
- Imperato-McGinley, J., Guevro, L., Gauteri, T. *et al.* (1974). Steroid 5-alpha reductase deficiency in man: an inherited form of pseudohermaphroditism. *Science*, **186**, 1213-1215.
- Jardin, A., Bensadoun, H., Delauche-Cavallier, M. C. *et al.* (1991). Alfuzosin for treatment of benign prostatic hypertrophy. *Lancet*, **337**, 1457-1461.
- Kirby, R. S., Copptager, S. W., Corcoran, M. O. *et al.* (1987). Prazosin in the treatment of prostatic obstruction. A placebo-controlled study. *Br. J. Urol.*, **60**, 136-142.
- Pelerson, E. L. (1946). A study of the effect of stilbestrol therapy on the size of the benignly enlarged prostate gland. *J. Urol.*, **55**, 73-78.
- Peters, C. A. and Walsh, P. C. (1987). The effect of nafarelin acetate, a luteinising hormone releasing agonist, on benign prostatic hyperplasia. *N. Engl. J. Med.*, **317**, 599-604.
- Price, H., McNeal, J. E. and Stamey, T. A. (1990). Evolving patterns of tissue composition in benign prostatic hyperplasia as a function of specimen size. *Hum. Pathol.*, **21**, 578-585.
- Resnick, M. L. (1990). *Prostatic ultrasonography*. P. 73. B. C. Decca.
- Roos, N. P., Wenberg, J. E., Malenka, D. J. *et al.* (1989). Mortality and reoperation after open and transurethral resection of the prostate for benign prostatic hypertrophy. *N. Engl. J. Med.*, **320**, 1120-1124.
- Scott, W. W. and Wade, J. C. (1969). Medical treatment of benign nodular hyperplasia with cyproterone acetate. *J. Urol.*, **101**, 81-85.
- Shimazaki, J., Kurihara, H., Ho, Y. *et al.* (1965). Testosterone metabolism in the prostate. *Gunma J. Med. Sci.*, **14**, 313-333.
- Siliteri, P. K. and Wilson, J. D. (1970). Dihydrotestosterone in prostatic hypertrophy. *J. Clin. Invest.*, **49**, 1737-1745.
- Stone, N., Ray, P. S. and Smith, J. A. (1989). A double-blind randomized controlled study of the effect of flutamide in benign prostatic hypertrophy: clinical efficacy. *J. Urol.*, **141**, 2409.
- Stoner, E. (1990). The clinical development of a 5-alpha reductase inhibitor, finasteride. *J. Steroid. Biochem. Molec. Biol.*, **37**, 375-378.
- Walsh, P. C., Hutchings, A. M. and Ewing, L. L. (1983). Tissue content of dihydrotestosterone in human prostatic hyperplasia is not supra-normal. *J. Clin. Invest.*, **72**, 1772-1777.
- Wolf, H. and Madson, P. O. (1968). Treatment of benign prostatic hypertrophy with progestational agents: a preliminary report. *J. Urol.*, **99**, 980-985.

The Authors

- R. S. Kirby, MA, MD, FRCS (Urol), Consultant Urologist.
Jenny Bryan, SRN, Senior Research Nurse, Department of Urology.
I. Earcley, FRCS, Senior Registrar, Department of Urology, Norfolk and Norwich Hospital, Norwich.
T. J. Christmas, FRCS, Senior Registrar, Department of Urology.
S. Liu, FRCS, Research Fellow, Department of Urology.
S. A. V. Holmes, FRCS, Research Registrar, Department of Urology.
J. A. Vale, FRCS, Registrar, Department of Urology.
K. Shanmuganathan, FRCS, Senior Registrar, Department of Radiology.
Judith A. Webb, MD, FRCS, Consultant Radiologist.

Requests for reprints to: R. S. Kirby, Department of Urology, St Bartholomew's Hospital, West Smithfield, London EC1A 7BE.

Long-term Results of Treatment of Urethral Injuries in Males Caused by External Trauma

B. J. JENKINS, D. F. BADENOCH, C. G. FOWLER and J. P. BLANDY

Department of Urology, Royal London Hospital, London

Summary—Of 134 males with traumatic rupture of the urethra seen between 1967 and 1989, 10 have been lost to follow-up and 124 have been followed up for 1 to 22 years (mean 8); 100 patients had a pelvic fracture (3 with associated rectal injury) and 24 had perineal injuries. Prior to referral 31 patients (25%) had undergone treatment in addition to suprapubic cystostomy. Wherever possible, strictures were managed by optical urethrotomy (33) or intermittent dilatation (4). In 2 patients only a suprapubic cystostomy was possible. Skin inlay urethroplasty in 1 or 2 stages was performed in 75 cases, an end-to-end anastomosis with or without resection of the symphysis pubis in 7 and a scrotal tube pull-through in 3.

The immediate and long-term results depended on the severity of the original injury. With minimal displacement the management was simple and the long-term prognosis good, a single urethrotomy being sufficient in 22 patients. Where there was considerable displacement the initial management was more difficult and there was a high incidence of long-term complications: of 73 patients treated by urethroplasty or end-to-end anastomosis, significant post-operative infection occurred in 11 (15%) and restenosis in 15 (20%), of whom 7 required a revision urethroplasty. Data in respect of potency were recorded in 80 patients: 28 of these were impotent, 20 of the 28 having sustained an injury with considerable displacement.

In contrast to the continuing controversy over the initial management of the ruptured urethra, little attention has been given to the long-term outcome, although for the patient and his medical and legal advisers this is important in determining appropriate follow-up and fair compensation.

Patients and Methods

We reviewed the records of 134 male patients admitted to the Royal London Hospital between 1967 and 1989 with injuries to the urethra caused by external violence, *i.e.* a fall astride injury or fracture of the pelvis. In 10 the long-term details were incomplete; 124 patients were followed up from 1 to 22 years (mean 8). The age of the patients

ranged from 16 to 81 years (mean 28). Only 18 of these 124 patients (14.5%) presented with an acute injury. The remainder were referred after initial treatment elsewhere.

Classification of injury

Fall astride injury caused the urethral rupture in 24 patients (19%). In 100 patients (81%) the urethral injury followed fractures of the pelvis: these were subdivided into 2 main groups.

Type I. Minimal displacement of the injured urethra occurred in 25 patients, usually caused by antero-posterior or lateral compression of the bony pelvis with fractures of 2 or more of the ischiopubic rami (Fig. 1).

Type II. In 75 cases there was gross dislocation of the bony fragments and a wide separation of the

Read at the 46th Annual Meeting of the British Association of Urological Surgeons in Scarborough, July 1990.



Fig. 1 Type I pelvic fracture.

ends of the ruptured urethra (Fig. 2). In 3 patients there was an associated injury of the rectum.

Treatment

In all cases a suprapubic cystostomy was performed at first.

Fall astride injuries

Of the 24 patients in this group, 20 (83%) required only optical urethrotomy (16) or dilatation (4). Urethroplasty was needed in 4 cases.



Fig. 2 Type II pelvic fracture.

Pelvic fracture injuries

This group included 100 patients, 31 of whom had undergone some previous attempt at urethral reconstruction before being referred.

Type I injuries

In 25 patients with minimal displacement of the urethral segments, the 2 ends were usually separated only by a relatively narrow septum of scar tissue. An attempt was always made to divide this endoscopically, using a rigid or fiberoptic endoscope passed retrogradely via the suprapubic tract to assist the urethral operator (Fowler, 1984). This was successful in 17 of the 25 patients (68%), but in 8 it was impossible to find a way through the scar tissue and urethroplasty was required. In the early part of this series a 2-stage scrotal flap urethroplasty was used (Blandy *et al.*, 1968); later this was replaced by the 1-stage dartos-pedicled island patch procedure (Blandy and Singh, 1975) or an end-to-end anastomosis through a perineal approach (Blandy, 1986).

Type II injuries

Of the 75 patients with severe displacement of the severed ends of the urethra there were 2 who underwent only a suprapubic cystostomy and died of other multiple injuries shortly after admission.

Operative reconstruction was always more difficult in this group. In 64 cases a long skin inlay was used, either in 1 or 2 stages: in 3 patients the scrotal flap was formed into a tube and drawn up in imitation of Badenoch's pull-through operation (Badenoch, 1950; Blandy and Singh, 1972). In 3 recent cases an end-to-end anastomosis was performed with the resection of a small window from the inferior border of the symphysis pubis (Blandy, 1986).

In the 3 patients who had in addition a laceration of the rectum, the most important step in the early management was to establish a defunctioning colostomy as well as adequate urinary diversion (Blandy and Singh, 1972).

Results

The overall outcome reflected the severity of the original injury. In the 49 patients with perineal injuries or pelvic fracture with minimal displacement of the urethral segments, the initial management was straightforward (Table 1), the long-term complications rare and the outlook good; 4 patients needed occasional dilatation only. Of the 33 patients

Table 1 Original Definitive Treatment of Urethral Injury

	Perineal	Type I	Type II
Dilatation	4	—	—
Urethrotomy	16	17	—
Urethroplasty	4	8	73
Total	24	25	73*

*Excluded are 2 patients fit only for suprapubic cystostomy.

managed initially by optical urethrotomy, 22 required only a single urethrotomy; 11 needed further urethrotomies and 5 patients eventually went on to have a urethroplasty. Twelve patients in this group were treated initially by urethroplasty or end-to-end anastomosis; 2 of these required a revision urethroplasty after 2 and 5 years; 3 of the 49 patients (6%) developed an infective complication (Table 2).

In contrast, in the 73 patients who began with a widely dislocated pelvic fracture and who had to undergo a more difficult reconstruction, the long-term results were much worse. No fewer than 11 (15%) suffered more or less severe infective complications (e.g. septicaemia, calculi, epididymitis); restenosis occurred in 15 (20%), of whom over half were subsequently managed adequately by regular dilatation but 7 eventually needed a second urethroplasty.

Impotence in this series was not always recorded in the records. In the 80 charts where details were available, impotence was noted in 28 (35%); with 8 exceptions these were all patients with Type II fractures of the pelvis with gross displacement of the bony fragments signifying major soft tissue injury.

Table 2 Episodes of Significant Infection

	Perineal	Type I	Type II
Epididymitis	2	1	6
Septicaemia	—	—	2
Haematoma	—	1	3
Wound infection	—	—	2
Hairball	—	—	2
Fistula	—	—	2
Necrosis of wound edge	—	—	1

Discussion

It is not the purpose of this report to comment upon the initial management of these patients—our concern was with their aftermath. It is acknowledged that the long-term prognosis may be very poor in some patients, with complications occurring many years after the original injury and treatment (Badenoch, 1968; Mitchell, 1968).

Infection and restenosis pose a continuing threat: up to 40% of patients, if followed up for long enough, may develop a post-urethroplasty stricture (Dobrowolski, 1982). Impotence—varying largely with the severity of the original injury—is a serious disability. Half of the 44 patients treated by transpubic urethroplasty at the Mayo Clinic for post-traumatic prostatomembranous strictures developed permanent erectile dysfunction (Zinke and Furlow, 1985).

For those who wish to undertake the burden of improving the initial and subsequent management of these young men there are still major obstacles to overcome.

References

- Badenoch, A. W. (1950) A pull-through operation for impassable traumatic stricture of the urethra. *Br. J. Urol.*, **22**, 404–409.
- Badenoch, A. W. (1968). Traumatic stricture of the urethra. *Br. J. Urol.*, **40**, 671–676.
- Blandy, J. P. (1986). Operations on the male urethra. In *Operative Urology*. Second edition. Chapter 14, pp 206–237. Oxford: Blackwell Scientific Publications.
- Blandy, J. P. and Singh, M. (1972). Fistulae involving the adult male urethra. *Br. J. Urol.*, **44**, 632–643.
- Blandy, J. P. and Slagh, M. (1975). The technique and results of one-stage island patch urethroplasty. *Br. J. Urol.*, **47**, 83–87.
- Blandy, J. P., Singh, M. and Treslender, G. C. (1968). Urethroplasty by scrotal flap for long urethral strictures. *Br. J. Urol.*, **40**, 261–267.
- Dobrowolski, Z. (1982). Long-term results of surgical treatment of post-traumatic posterior urethral strictures by Solovov's method. *J. Urol.*, **128**, 700–702.
- Fowler, C. G. (1984). Flexible urethrocystoscopy. *Br. J. Urol.*, **56**, 304–307.
- Mitchell, J. P. (1968). Injuries to the urethra. *Br. J. Urol.*, **40**, 649–670.
- Zinke, H. and Furlow, W. L. (1985). Long-term results with transpubic urethroplasty. *J. Urol.*, **133**, 605–606.

The Authors

B. J. Jenkins MChir, FRCS, Senior Registrar.
D. F. Badenoch, DM, MCh, FRCS(Urol), Consultant Urologist.
C. G. Fowler, MRCP, FRCS(Urol), Consultant Urologist.
J. P. Blandy, DM, MCh, FRCS, FACS, Professor.

Requests for reprints to: J. P. Blandy, Department of Urology, Royal London Hospital, Whitechapel, London E1 1BB.

Treatment of Hydrocele: Randomised Prospective Study of Simple Aspiration and Sclerotherapy with Tetracycline

G. BREDI, A. GIUNTA, L. GHERARDI, D. XAUSA, P. SILVESTRE and A. TAMAI

Department of Urology, Community Hospital, Bassano del Grappa, Italy

Summary—Following reports in the literature on the efficacy of tetracycline sclerotherapy in the treatment of hydroceles, we carried out a randomised prospective study of 45 patients (50 hydroceles), comparing simple evacuation with tetracycline sclerotherapy. The results revealed no statistically significant difference in the percentage of success between the 2 groups, but complications were more common in the patients treated with tetracycline. The good results reported by other authors in non-randomised studies are, therefore, not confirmed.

Surgical repair is the standard treatment of communicating and multilocular hydroceles (Steward, 1979), although this may lead to complications such as haematoma (0–17%), infection (2–10%) and relapse (5–10%) (Lord, 1964; Moloney, 1975). In many centres this is treated by a short period of hospitalisation. Other (older) methods, such as aspiration (a simple and rapid procedure), are now used less often because they are rarely curative. In recent times, some success has been achieved by sclerotherapy using tetracycline (Bødker *et al.*, 1985; Badenoch *et al.*, 1987; Levine and DeWolf, 1988) or other sclerosing agents (Hellström *et al.*, 1988) administered into the vaginal sac. Bødker *et al.* (1985) reported a 50% success rate after a single injection of tetracycline. Badenoch *et al.* (1987) claimed a success rate of 33% and Levine and DeWolf (1988) reported successful results in up to 75% of patients. The sclerosing effect of tetracycline is thought to be due to the low pH of the solution which induces a significant cell reaction with fibrosclerosis and adhesions of the membranes of the tunica vaginalis (Robinson and Bolooki, 1972; Bødker *et al.*, 1985). The findings of Levine and DeWolf (1988) seem particularly striking. Since we had no experience of tetracycline sclerotherapy in the treatment of hydroceles and given the lack of comparative studies on the relationship between simple aspiration and sclerotherapy, we carried out

a prospective randomised study to assess the efficacy of sclerotherapy with tetracycline.

Patients and Methods

From October 1989 to October 1990 a randomised study was carried out on 45 patients with a total of 50 hydroceles undergoing initial treatment. Some patients complained of testicular pain, others of genital volume. All were examined by scrotal transillumination and, in certain cases, by scrotal ultrasonography. No patient was allergic to tetracycline and no inguinal hernias or epididymal cysts were detected. After sterilisation of the scrotal skin with Betadine and infiltration of the spermatic cord with 10 ml of a mixed solution (2% mepivacaine and 0.5% bupivacaine), 25 hydroceles (group A) were treated by simple aspiration with a 16 gauge silicone-coated cannula, while 25 hydroceles (group B) were treated by the same aspiration procedure together with sclerotherapy with tetracycline (500 mg in 5 ml physiological solution) injected directly into the vaginal sac through the cannula while monitoring the patient's arterial pressure. Group A was composed of 24 patients aged between 15 and 86 years (mean 51.9) with hydrocele volume of 45 to 420 ml (mean 107.4). One patient had bilateral hydroceles. Group B included 21 patients aged between 18 and 83 years (mean 52.4) with a hydrocele volume of 50 to 500 ml (mean 170.2). Four patients had bilateral hydroceles. The patients

were kept under observation for approximately 2 h and then discharged. Subsequent check-ups were carried out after 15 days, and then monthly for 3 consecutive months, and finally at intervals of 6 and 12 months (from a minimum of 4 to a maximum of 16 months). The drained hydrocele liquid was sent for physico-chemical, bacteriological and cytological examination and a search for Koch's bacillus. In the case of relapse, resection or eversion of the tunica vaginalis was carried out, depending on the presence or absence of a thickened vaginalis.

Results

In group A (simple aspiration) there were 5 cases of complete healing (20%) and 1 of partial healing (4%) (50% reduction in the volume of the hydrocele); 19 patients (76%) relapsed after a minimum of 15 and a maximum of 210 days (mean 30.8). None of the patients complained of pain. Thirteen relapses (52%) were treated by eversion of the tunica vaginalis with excellent results; 6 relapsed patients refused further treatment. In group B (sclerotherapy with tetracycline) there were 5 cases of complete (20%) and 5 of partial healing (20%); 15 patients (60%) relapsed after a minimum of 20 and a maximum of 120 days (mean 36). Thirteen patients (52%) complained of mild to severe pain after treatment (ranging from 5 h to 30 days) that involved analgesics. One patient had a transitory lipothymic episode at home and 2 developed epididymitis. Another patient with a recurrent hydrocele refused treatment. Fourteen recurrent hydroceles were treated by resection or eversion of the tunica vaginalis, all with good results. In 7 patients with a markedly thickened tunica vaginalis, bleeding easily and with the surface of the testis covered by whitish fibrinous patches, samples of the tunica vaginalis were examined histologically and in all cases the diagnosis was chronic pachy-vaginalitis. The results of the physico-chemical, bacteriological and cytological analysis and the search for Koch's bacillus were similar in all cases.

Discussion

Drainage of the hydrocele without sclerotherapy is not curative and the relapse rate is high. It is best used as a palliative procedure in patients whose general condition is poor. Despite the excellent results reported in the literature, we found that treatment by aspiration coupled with tetracycline sclerotherapy led to a 60% failure rate, with only 20% of patients achieving complete healing. A comparative analysis of the results obtained by the

2 groups (χ^2 test) revealed no statistically significant difference between them as regards the efficacy of treatment. In addition, 52% of patients undergoing sclerotherapy reported mild to severe pain, sometimes for prolonged periods, and 8% developed epididymitis. Our findings are in contrast with those of Bødker *et al.* (1985) (9/10 patients healed, 50% of them after a single injection), and Levine and DeWolf (1988) (93% success rate, 75% after a single injection). Our findings are closer to those of Badenoch (1987) (7/15 relapses, a 33.3% success rate and a 20% partial resolution of the hydrocele). Badenoch *et al.* (1987) also confirmed our finding that pain (sometimes abdominal) was a frequent occurrence (in 46.7% of patients) and claimed that "the use of regional anaesthesia helped but pain remained a distressingly common complaint following the procedure. We have abandoned this form of treatment." In our opinion, surgical repair (carried out on an out-patient basis), despite being associated with complications, is the preferred method of treatment for hydrocele. Its results are good and complications are rare.

References

- Badenoch, D. F., Fowler, C. G., Jenkins, B. J. *et al.* (1987). Aspiration and instillation of tetracycline in the treatment of testicular hydrocele. *Br. J. Urol.*, **59**, 172-173.
- Bødker, A., Sommer, W., Andersen, J. T. *et al.* (1985). Treatment of hydrocele of the testis with aspiration and injection of tetracycline. *Br. J. Urol.*, **57**, 192-193.
- Hellström, P., Tammela, T., Kontturi, M. *et al.* (1988). Ethanolamine oleate as a sclerosant for testicular hydroceles and epididymal cyst. *Br. J. Urol.*, **62**, 445-448.
- Levine, L. A., and DeWolf, W. C. (1988). Aspiration and tetracycline sclerotherapy of hydroceles. *J. Urol.*, **139**, 959-960.
- Lord, P. H. (1964). A bloodless operation for the radical cure of idiopathic hydrocele. *Br. J. Surg.*, **51**, 914-916.
- Moloney, G. E. (1975). Comparison of results of treatment of hydrocele and epididymal cysts by surgery and injection. *Br. Med. J.*, **3**, 478-479.
- Rubinson, R. M. and Bolooki, H. (1972). Intrapleural tetracycline for control of malignant pleural effusions: a preliminary report. *South. J. Med.*, **65**, 847-849.
- Stewart, B. H. (1979). Surgery of the scrotum and its contents. In *Campbell's Urology*, ed. Harrison, J. H., Gittes, R. F., Perlmutter, A. D., Stamey, T. A. and Walsh, P. C. Fourth edition Volume III. Chapter 84, pp. 2473-2498. Philadelphia: Saunders.

The Authors

G. Breda, MD, Chief of Department of Urology.
A. Giunta, MD, Assistant.
L. Gherardi, MD, Senior Assistant.
D. Xausa, MD, Senior Assistant.
P. Silvestre, MD, Assistant.
A. Tamai, MD, Assistant.

Requests for reprints to: G. Breda, Department of Urology, Community Hospital, Bassano del Grappa (VI), Italy.

New Approach to the Management of Fournier's Gangrene

C. A. ATTAH

Department of Surgery, University of Nigeria Teaching Hospital, Enugu, Nigeria

Summary—A new method of treating Fournier's gangrene is described in 13 patients. There was no mortality and the average hospital stay was 10 days. Considerable gain in man-hours and expense was recorded when compared with the old method of treatment with antibiotics and wound debridement.

Fournier's gangrene is rare (Toktas *et al.*, 1988) but commoner among Nigerian Igbos than other races. It occurs more frequently in older males, but Evbuomwan and Aliu (1984) and Adams *et al.* (1990) described its occurrence in 1-month-old and 4-year-old boys. In Nigeria, the local herbalist or medicine-man is usually consulted first, and only after fruitless efforts with herbal concoctions is the orthodox medical practitioner consulted.

The cause of the disease is not clear, but it is often superimposed on a filarial scrotum in our geographical area. It has also been associated with urogenital pathology (Fahal and Hassan, 1988; Octavio Castillo and Carlos Martinez, 1990), minor trauma or a procedure (Chantarasak and Basu, 1988) in the genital area and after aggressive treatment of haematological disorders (Berg *et al.*, 1986). Khan *et al.* (1985) reported the condition in a patient with sigmoid diverticulitis and Gaeta *et al.* (1991) also described it following perforated appendicitis. Joo and Peters (1985) described its occurrence with diabetes mellitus and Van der Meer *et al.* (1990) thought it might be a human form of the Schwartzman phenomenon.

The diagnosis is generally easy and it may involve not only the scrotum but also the perineum, penis and abdomen (Schneider *et al.*, 1986; Mulholland *et al.*, 1990).

Hitherto the management has been surgical debridement and antibiotics (Leenen and Van der

Werken, 1991) until the wound becomes clean enough for coverage. Hyperbaric oxygen has also been noted to be beneficial (Lucca *et al.*, 1990; Riegals-Nielsen *et al.*, 1984; Radaelli *et al.*, 1987). The choice of antibiotics has to reflect the involvement of several organisms (Joo and Peters, 1985; Schneider *et al.*, 1986). Kottasz *et al.* (1988) advocate aggressive surgery. However, treatment by debridement, antibiotics and other supportive measures is time-consuming, costly and tedious. Our patients are usually rural farmers who can ill afford the time or the money. As a result, a new approach has been developed.

Patients and Methods

Thirteen patients with Fournier's gangrene were managed over a 4-year period in Attah Memorial Hospital.

Physical examination included a search for filarial dermatitis, especially in what remained of the scrotum, and other areas of the body. Investigations included full blood count, urine analysis, urine culture and sensitivity, wound swab for culture and sensitivity and fasting blood sugar. Patients who presented with fever had blood cultures examined for malaria parasites. Night bloods and skin snips for microfilaria were also taken.

Treatment was usually started with broad spectrum antibiotics while awaiting the result of cultures. Analgesics and antipyretics were also given. The wounds were dressed several times daily.

As soon as the patient was stabilised, usually within 2 days of admission, he was taken to the operating theatre for the appropriate surgery, which consisted of radical amputation of the scrotum beyond the involved area, safeguarding the testes. The wound was usually closed primarily and high doses of the appropriate antibiotics were administered until removal of the skin stitches. Sometimes the patients were discharged before stitch removal. Antimalarial and antimicrobial treatment was given if necessary.

Results

The patients varied in age from 42 to 76 years (Table 1); 11 presented with fungating ulcers and 2 had marked scrotal oedema with skin blisters. The physical findings are shown in Table 2 and laboratory findings in Tables 3 and 4.

Nine patients were discharged within 10 days of admission and all achieved primary healing of the wounds. The wound broke down in 2 patients and needed secondary closure but both patients were discharged home before the stitches were removed. Two patients had minor wound infections followed up in the out-patient clinic. No mortality was recorded.

Table 1 Patients' Ages

Age (years)	No.
40-49	1
50-59	2
60-69	7
70-79	3
Total	13

Table 2 Clinical Findings

Findings	No
Swelling	12
Ulcer	11
Blisters	2
Fever	7
Hypertension	4
Congestive heart failure	3
Onchocerca nodules	3
Onchocerca dermatitis	1

Table 3 Laboratory Findings

Laboratory Findings	No.
Malaria parasite	4
Microfilaria bancrofti	5
Diabetes mellitus	2
Urinary tract infection	3

Discussion

Whereas conservative treatment of Fournier's gangrene requires hospitalisation for 6 weeks, this new method requires about 10 days. Because of the difference between the old conservative and the new aggressive method of treatment, a randomisation study was thought to be unethical.

In the patients described, the disease was limited to the scrotum and not allowed to extend to other adjoining areas, which often happened with the debridement method. Because of the limited areas involved, plastic surgery was not required (Hesselfeldt *et al.*, 1988; Hallock, 1990).

Table 4 Results of Culture

Patient	Results of culture	Urine culture	Blood culture
O.J	<i>Staph aureus</i>	No growth	Negative
U.O.	<i>Staph. aureus</i> + <i>E coli</i>	No growth	Negative
M.O	<i>Klebsiella</i> spp.	No growth	Negative
A.C.	<i>E coli</i> + <i>Staph. epidermidis</i>	<i>E coli</i>	Negative
O.A.	<i>Staph. aureus</i> + coliform bacillus	<i>Staph. aureus</i>	<i>Staph. aureus</i>
U.A	No growth	No growth	No growth
J.C	<i>Strep. faecalis</i>	Coliform bacillus	No growth
J.U	<i>Staph. aureus</i>	No growth	No growth
M.E.	<i>Ps aeruginosa</i>	No growth	No growth
M.M	No growth	No growth	No growth
F.A.	<i>Ps. aeruginosa</i>	<i>Ps aeruginosa</i>	No growth
O.N.	<i>Staph epidermidis</i>	No growth	No growth
S.I.	Coliform bacillus	<i>E. coli</i>	<i>E. coli</i>
O.M	No growth	No growth	No growth

References

- Adams, J. R., Jr., Mata, J. A., Venable, D. D. *et al.* (1990). Fournier's gangrene in children. *Urology*, **35**, 439–441.
- Berg, A., Armitage, J. O. and Burns, C. P. (1986). Fournier's gangrene complicating aggressive therapy for hematologic malignancies. *Cancer*, **57**, 2291–2294.
- Chantarasak, N. D. and Basu, P. K. (1988). Fournier's gangrene following vasectomy. *Br. J. Urol.*, **61**, 538–539.
- Eybuomwan, I. and Aliu, A. S. (1984). Acute gangrene of the scrotum in one month old child. *Trop. Geogr. Med.*, **36**, 299–300.
- Fahal, A. H. and Hassan, M. A. (1988). Fournier's gangrene in Khartoum. *Br. J. Urol.*, **61**, 451–454.
- Gaeta, M., Volta, S., Minutoli, A. *et al.* (1991). Fournier's gangrene caused by perforated retroperitoneal appendix. *A.J.R.*, **156**, 341–342.
- Hallock, G. G. (1990). Scrotal reconstruction following Fournier's gangrene using the medical thigh fasciocutaneous flap. *Ann. Plast. Surg.*, **24**, 86–90.
- Hesselfeldt-Nielsen, J., Bang-Jensen, E. and Riegels-Nielsen, P. (1988). Scrotal reconstruction after Fournier's gangrene. *Ann. Plast. Surg.*, **17**, 310–316.
- Joo, P. and Peters, W. J. (1985). Fournier's gangrene. *Can. J. Surg.*, **28**, 180–182.
- Khan, S. A., Smith, N. L., Goadar, M. *et al.* (1985). Gangrene of male external genitalia in a patient with colo-rectal disease. *Dis. Colon Rectum*, **28**, 519–522.
- Kottasz, S., Siller, G. and Brousl, E. (1988). Fournier's gangrene: experience in the treatment of the male genitals. *Int. Urol. Nephrol.*, **20**, 505–511.
- Leenen, L. P. and Van der Werken, C. (1990). Fournier's gangrene. *Acta Chir. Belg.*, **91**, 204–206. (English abstract).
- Lucca, M., Unger, H. D. and Devenney, A. M. (1990). Treatment of Fournier's gangrene with adjunctive hyperbaric oxygen therapy. *Am. J. Emerg. Med.*, **8**, 385–387.
- Mulholland, C. K., Deamond, T., Ritchie, A. *et al.* (1990). Fournier's gangrene: two unusual cases. *Ulster Med. J.*, **59**, 90–92.
- Octavio Castillo, C. and Carlos Martinez, S. (1990). Necrotising perineal phlegmon (Fournier's gangrene). *Actas Urol. Esp.*, **13**, 381–383. (English abstract).
- Radaelli, F., Della Volpe, A., Colombi, M. *et al.* (1987). Acute gangrene of the scrotum and penis in four hematologic patients. The usefulness of hyperbaric oxygen therapy in one case. *Cancer*, **60**, 1462–1464.
- Riegels-Nielsen, P., Bang-Jensen, E., Hesselfeldt-Nielsen, J. *et al.* (1984). Fournier's gangrene: 5 patients treated with hyperbaric oxygen. *J. Urol.*, **132**, 918–920.
- Schneider, P. R., Russel, R. C. and Zook, E. G. (1986). Fournier's gangrene of the penis: a report of two cases. *Ann. Plast. Surg.*, **17**, 87–90.
- Toktas, G., Uysal, Z., Erkan, I. *et al.* (1988). Fournier's gangrene: report of six cases. *Mikrobiyol. Bul.*, **22**, 72–75. (English abstract).
- Van der Meer, J. B., Van der Meer Wal, T., Bos, W. H. *et al.* (1990). Fournier's gangrene: the human counterpart of the local Shwartzman phenomenon? *Arch. Dermatol.*, **126**, 1376–1377.

The Author

C. A. Attah, MD, FACS, FRCS(C), Consultant Urologist and Senior Lecturer, College of Medicine, University of Nigeria Teaching Hospital, Enugu, Nigeria.

Vacuum Constriction Devices: Second-line Conservative Treatment for Impotence

H. W. GILBERT and J. C. GINGELL

Department of Urology, Southmead Hospital, Bristol

Summary—Intracavernosal pharmacotherapy is not a universally successful treatment of impotence. Vacuum constriction devices are reported to be an effective non-operative alternative. This study investigated the value of these devices in 45 impotent men who had failed to become established on intracavernosal papaverine. Although 38 were able to obtain an erection-like state using a vacuum constriction device, only 12 were able to enjoy satisfactory sexual intercourse and, of these, just 7 men found them of sufficient benefit to warrant purchase. Success is not predicted by aetiology. Vacuum constriction devices are of some use, but a trial period of use should be allowed to each patient before purchase.

Although intracavernosal pharmacotherapy (ICP) is a successful first-line treatment for a large proportion of impotent men, a significant number fail to respond because of a haemodynamic abnormality (Juenemann and Alken, 1990). Although such abnormalities may be corrected by either revascularisation (Zorgniotti and Lizza, 1988), venous ligation (Lewis, 1990) or, if all else fails, the insertion of penile prostheses, some patients, particularly the elderly, will decline operative intervention. In addition, those who respond to ICP may not wish to inject themselves either because of a fear of needles or because they find that the process of injection is cumbersome (Althof *et al.*, 1989).

Although vacuum constriction devices (VCD) were described by Lederer as early as 1917, they did not become widely available until the 1970s. Their principle is that penile engorgement is produced within a suction chamber and is then maintained by a soft constriction ring placed around the base of the penis. This study was designed to evaluate the effectiveness of VCDs in overcoming impotence in men who either failed to respond to or to accept ICP.

Patients and Methods

Forty-five impotent men (age range 35–69 years) who had failed to become established on ICP (maximum dose 60 mg papaverine) were consecutively recruited from the impotence clinic. All had been unable to perform sexual intercourse owing to erectile failure for at least 6 months (range 6–108). All were established in long-term sexual relationships (range 4–45 years). In each case the aetiology of the erectile failure was determined according to history, examination, results of an intracavernosal papaverine test, duplex Doppler scanning (Gilbert *et al.*, 1991) and, where necessary, pharmacocavernosometry. On this basis the principal aetiological factor was arteriopathy in 29 cases (64%), exclusively venous leakage in 3 (7%) and neuropathy was implicated in 7 (16%). In the remaining 6 cases (13%) impotence was, in the absence of any evidence of organic disease, presumed to be due to principally psychogenic factors.

The use of VCDs was discussed with each patient and all agreed to participate in the study. Each patient was instructed in the use of the VCD (Response[®]; Owen Mumford, Woodstock, UK) by one of the investigators (H.G.). A video demonstration was available to reinforce this. Each patient then took the device home but was asked to contact the clinic if any practical problems arose. After 3

months a questionnaire, to be completed anonymously, was sent to each patient and, separately, to his sexual partner. One month later each patient returned to the clinic for review by interview.

Results

Using the device, 38 men (83%) were able to achieve a state of penile tumescence of sufficient rigidity to allow sexual intercourse. The remaining 7 (17%) were unable to produce a sustained state of tumescence; 3 found the ring painful and, in 4 cases, even the smallest (10 mm) did not provide sufficient constriction.

Of the 38 men who were able to induce an erection-like state, 26 (68%) did not wish to purchase the device; 13 (50%) complained of some loss of feeling or disordered sensation prior to or during intercourse and 13 couples considered that the production of an erection was so mechanical, time-consuming or contrived that it frequently led to a loss of desire.

Twelve of the 45 men who participated in this trial (27%) found the VCD enabled satisfactory intercourse for both themselves and their respective partners. The principal aetiological factor contributing to their impotence was arterial disease in 7 (duplex ultrasonography; peak flow velocity <25 cm/s, arterial calibre <0.8 mm), venous leakage in 1 (pharmacocavernosometry; maintenance flow rate >30 ml/min), neurological disease (multiple sclerosis) in 1 and psychological disturbance in the remaining 3.

Despite the incentive of the resumption of sexual intercourse, 5 men felt that the VCD was too expensive to be of value. Thus only 7 of those who entered the study (16%) purchased a VCD for continued use. All had satisfactory sexual intercourse at least once a week over the study period and continued to use their VCD regularly after this (mean follow-up 7 months). None of these patients experienced any difficulty with orgasm or ejaculation.

All participants were asked whether they thought that VCDs should be offered to other men with erectile problems; 85% believed so.

Discussion

Since its introduction, intracavernosal pharmacotherapy has been successful in treating a large number of men suffering from impotence. A significant number with a vascular aetiology will fail to respond. In addition, some men who respond

adequately to ICP decline its use because they are not prepared to self-inject. Although the surgical insertion of penile prostheses is a therapeutic option, many dismiss it as too invasive. Vacuum constriction devices have been available for several years and several reports have indicated that they are a very successful method of treating impotence. The existing literature in support of this statement is, however, unsatisfactory. Witherington (1989), in reviewing patients' responses to a questionnaire issued by the manufacturer, found that 77% used the device regularly. This statistic was derived from only 11% of those who purchased a device. Wiles (1986), in a study involving 10 patients, found that 6 were able to have regular intercourse with the help of a VCD, a figure which compares very favourably with that reported in this study. Higher response rates may be expected in an unselected group of patients who are offered VCDs exclusively; in this study all therapeutic options were discussed with each patient.

The Response^R VCD is similar in design and function to other commercially available products. It has a robust, manually operated pump, a hygienic perspex cylinder and a range of constriction rings which are easily mounted on the cylinder with the loading cone. As with other devices, a battery-operated pump is available for those who lack strength or manual dexterity.

It is important to inform the patient intending to try a VCD that a state of penile congestion is produced which, although suitable for intercourse, is not a normal erection (Nadig *et al.*, 1986). Otherwise inappropriately high expectations may be raised. A specific cause of failure in some men is flaccidity proximal to the constricting ring causing a hinge-like instability of the tumescent penis.

VCDs are safe and there are few contraindications to their use (Nadig, 1990). All patients will suffer from some minor petechiae and VCDs should, therefore, be used with caution (if at all) in those receiving anticoagulant medication (Walden, 1986). No significant complications associated with the use of VCDs have been reported. Patients are warned not to wear the constriction ring for longer than 30 min in order to avoid the possibility of ischaemic damage to the cavernosal tissues. Constriction rings do not invariably reduce the penile circulation time but, whilst the degree and duration of reduced flow which produce significant hypoxia remain uncertain, this rule should be adhered to (Katz *et al.*, 1990).

Aetiology does not predict success with VCDs. However, a patient's motivation—or that of his

partner—is extremely important in the management of erectile dysfunction. This is particularly evident in patients who fully respond to intracavernosal pharmacotherapy but who decline to be taught self-injection or discontinue its use after a short time. We feel that a similar lack of motivation, coupled with dissatisfaction with the quality of erections and the method by which they are produced, explains the high drop-out rate found in this study. In support of this, only 1 patient has resumed self-injection and only 2 await the insertion of penile prostheses.

It has not been possible to identify a specific aetiological group of impotent men who are unable to achieve an erection-like state with these devices. Although men with severe arterial disease or “end-organ failure” would seem less likely to respond, erections produced by VCDs have even been reported in men whose penile prostheses have been removed (Moul and McLeod, 1989). Because of this and their safety, VCDs can be tried in any patient suffering from erectile failure.

The majority of men, in our experience, failed to benefit from VCDs. A certain amount of practice and experimentation with different sizes of constriction rings is necessary to obtain the best results for each patient. For these 2 reasons, a trial period at home is required during which a patient and his partner can effectively evaluate the device.

Although some urologists and diabetologists have been successful in obtaining a limited number of these devices for their patients on a National Health Service budget, most men will have to purchase their own. Unfortunately, many of these men are retired or are on a low income and they find it difficult to justify the expense of a VCD. We are now able to offer these devices to impotent men from a small stock supplied by a manufacturer. Because the devices are issued from the clinic, it is possible to advise and supervise patients so that they can subsequently purchase a device only when they are entirely convinced of its benefit. For those patients who cannot afford to purchase a VCD, perhaps financial support should be available from

an appliance budget; the use of a VCD is more cost-effective than the insertion of penile prostheses under the National Health Service.

In conclusion, VCDs can be an effective alternative to intracavernosal pharmacotherapy. However, the purchase of a device before proper instruction, supervision and evaluation have been completed will in many cases lead to disillusionment and, possibly, to financial loss.

References

- Althof, S. E., Turner, L. A., Levine, S. B. *et al.* (1989). Why do so many people drop out from auto-injection therapy for impotence? *J. Sex. Marital Ther.*, **15**, 121–129.
- Gilbert, H. W., Desai, K. M. and Gingell, J. C. (1991). The non-invasive assessment of arteriogenic impotence: a comparative study. *Br. J. Urol.*, **67**, 512–516.
- Juennemann, K.-P. and Alken, P. (1990). Pharmacotherapy of erectile dysfunction: a review. *Int. J. Impotence Res.*, **1**, 71–93.
- Katz, P. G., Haden, H. T., Mulligan, T. *et al.* (1990). The effect of vacuum devices on penile hemodynamics. *J. Urol.*, **143**, 55–56.
- Lederer, O. (1917). *A Surgical Device*. US patent no. 1225341.
- Lewis, R. W. (1990). Venous ligation surgery for venous leakage. *Int. J. Impotence Res.*, **2**, 1–19.
- Moul, J. W. and McLeod, D. G. (1989). Negative pressure devices in the explanted penile prosthesis population. *J. Urol.*, **142**, 729–731.
- Nadig, P. W. (1990). Six years experience with the vacuum constriction device. *Int. J. Impotence Res.*, **1**, 55–58.
- Nadig, P. W., Ware, J. C. and Blumoff, R. (1986). Non-invasive device to produce an erection like state. *Urology*, **27**, 126–131.
- Walden, T. B. (1986). Osborn Erecaid (letter). *J. Urol.*, **136**, 689.
- Wiles, P. G. (1986). Successful non-invasive management of erectile impotence in diabetic men. *Br. Med. J.*, **296**, 161–162.
- Witherington, R. (1989). Vacuum constriction device for the management of erectile impotence. *J. Urol.*, **141**, 320–322.
- Zorgnotti, A. W. and Lizza, E. (1988). Non-prosthetic surgical strategies for impotence. *Urol. Radiol.*, **10**, 151–155.

The Authors

H. W. Gilbert, FRCS, Research Fellow.
J. C. Gingell, FRCS, Consultant Urologist.

Requests for reprints to: H. W. Gilbert, Department of Urology, Southmead Hospital, Westbury-on-Trym, Bristol BS10 5NB.

PAEDIATRIC UROLOGY

Ten-year Review of Treatment of the Undescended Testis in the West of Ireland

M. V. McKIERNAN, P. D. MURPHY and J. G. JOHNSTON

Department of Surgery, Castlebar General Hospital, Castlebar, Ireland

Summary—Advances continue to be made in the treatment of the undescended testis, and treatment recommendations are continually changing. We reviewed 543 patients admitted for treatment of undescended testes in the 10-year period 1977 to 1986. The side and position of the testis were recorded, the patient's age at operation and the procedure carried out. The presence of an associated inguinal hernia was noted. The necessity for reoperation was recorded and predisposing factors sought. We found the mean age at operation to be 9.5 years and this decreased significantly over the study period. Dartos pouch orchiopexy was the commonest operation (69%). No significant link was found between the procedure performed or the presence of a hernia and the need for further procedures; 2.7% of patients required such further procedures. A coherent classification of position is lacking for abnormally descended testes. We report a classification which we used to tackle this situation.

Cryptorchidism is a common problem, affecting 5.5% of normal birth weight (>2500 g) boys at birth. The incidence drops to 1.3% at 3 months. For the low birth weight boy (<2500 g) the corresponding figures are 28.7 and 4.6% (John Radcliffe Group, 1986). The incidence may be increasing (Chilvers *et al.*, 1984). It is the major risk factor for testicular carcinoma, a fact noted by LeCompte in 1851 (Johnson *et al.*, 1968). The true extent of the risk is unknown. Once estimated at 50 times normal (Gilbert and Hamilton, 1940), a more recent estimate is 8.8 (Morrison, 1976). Malignancy may arise despite orchiopexy (Cunningham, 1921). The relative risk has been estimated at 4.7 in unilateral and 9.3 in bilateral treated disease (Giwercman *et al.*, 1987). Another study found treated undescended testes (UDT) in 9.5% of testicular cancer patients (Pike *et al.*, 1986). This study shows also that operation does not reduce this risk. Such benefit has been suggested previously, when surgery was carried out before 6 years of age (Gehring *et al.*, 1974). An intra-abdominal testis runs 5 times the

risk of malignancy of an inguinal UDT (Martin and Menck, 1975) and 20% of malignancies occurring in association with UDTs affect the opposite testis (Johnson *et al.*, 1968). Fertility is markedly affected both by unilateral and bilateral cryptorchidism (Chilvers *et al.*, 1986). Evidence shows that these effects are progressive in the first 2 years after birth, becoming irreversible after this time (Mengel *et al.*, 1974). Bilateral cryptorchid individuals are infertile (Fonkalsrud, 1978) if untreated. Treatment before the age of 5 years produced 50% fertility in a study by Karcher (1967). Psychological studies have concluded that surgery should ideally be performed before the age of 6 months, or between 2 and 5 years (American Academy of Pediatrics, 1975). The importance of scrotal testes to a young boy has been recognised by Bell (1974).

The ideal age for orchiopexy is not yet clear and we must await the results of early orchiopexy now being undertaken. Even now the evidence points toward earlier operation than previously practised, probably before 2 years of age. We undertook a 10-year review of practice in this hospital, paying particular attention to trends in the age at operation.

Patients and Methods

The names of patients admitted for treatment of undescended testes between 1 January 1977 and 31 December 1986 were obtained from theatre log books. The case records were examined and useful information abstracted on to a standardised "questionnaire". In order to evaluate the position of the testes at operation a new classification (ADR system) was devised to replace the myriad of terms used in the notes. This working classification was as follows.

Testes were classified as Arrested, Deviated or Retractable. A testis found to be absent because of agenesis or atrophy was labelled A_0 . Intra-abdominal testes were labelled A_1 . Testes in the canal between the inguinal rings were designated A_2 . Those below the external ring were A_3 and those arrested at the inguinoscrotal junction were A_4 . A testis in the superficial inguinal pouch of Denis Browne was described as D_1 . All other ectopic testes were labelled D_2 . In these cases the concise position may be specified, *e.g.* D_2 groin, *etc.* A testis found to be retractile on examination or under anaesthesia was denoted 'R'. Statistical evaluation was carried out using standard error of means and probability tables. Fisher's exact test was used to evaluate the association between hernia and recurrence.

Results

In all, 554 names were obtained. Eleven charts were unobtainable, leaving 543 available for examination, a retrieval rate of 98%.

It was found that 262 patients (48.2%) had right UDT, 135 (24.9%) had left and 146 (26.9%) had bilateral UDT.

Age

The mean age at operation was 9.5 years (Fig. 1). The youngest patient was aged 6 months and the eldest 36 years. The mean age for each year of the study is shown in Figure 2. This decreased significantly ($P < 0.001$) from 1977 to 1986; 6.2% of patients were aged 5 years or less at operation. In 1977 there were no such patients, while in 1986 they made up 13.7%. This trend failed to reach statistical significance ($P = 0.0064$) but is favourable.

Operation

A total of 629 operations were performed, with yearly totals as shown in Figure 3. The methods

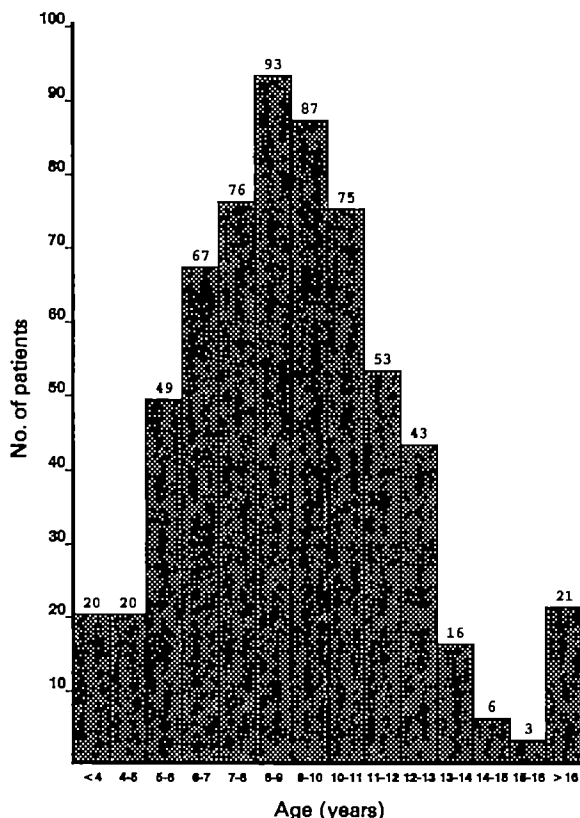


Fig. 1 Distribution of patients' ages. Actual numbers are shown. Total number of operations = 629.

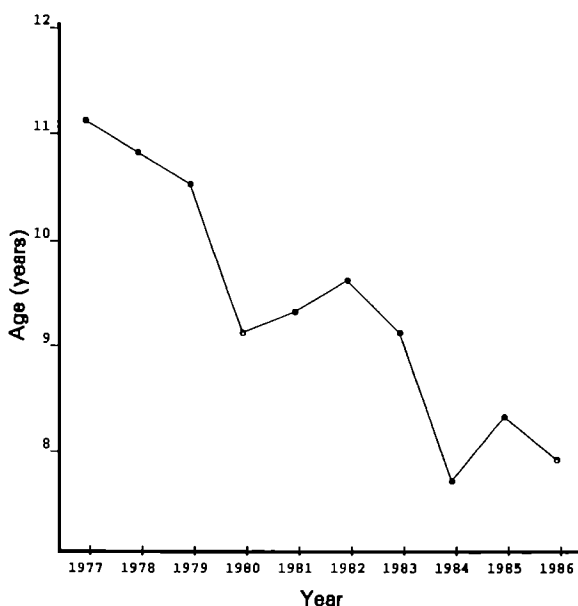


Fig. 2 Mean age at operation by year. Overall mean = 9.5 years. Decrease from 1977 to 1986 was statistically significant ($P < 0.001$).

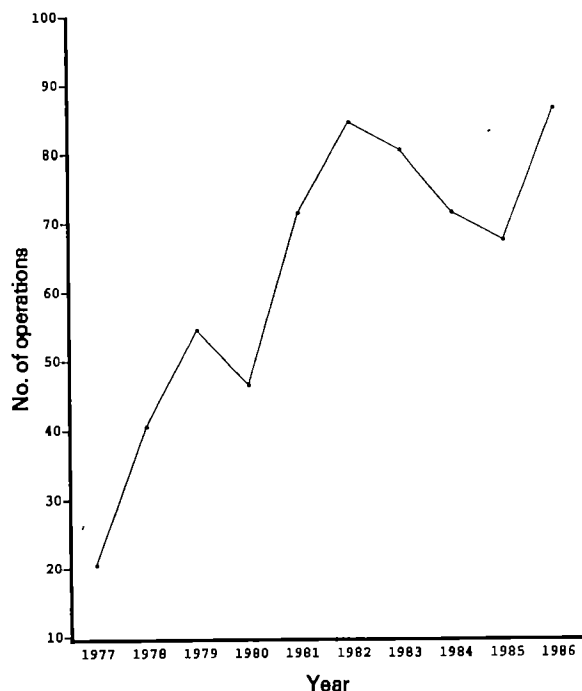


Fig. 3 Number of operations performed last year. Lowest 21 (1977), highest 89 (1986) (mean 62.9).

used are shown in Figure 4. Dartos pouch was the commonest (69%) with 11% being performed on both testes synchronously. Fixation to the scrotum (11.8%) involved catgut, silk or nylon according to the preference of the surgeon. Suture to the medial aspect of the thigh (9.2%), the favoured method of one surgeon at the beginning of the study period, is no longer practised. Other operations included orchiectomy (8), Keetley-Thorek operation, and negative explorations (see below). In 4.6% of cases the operative procedure was not specified.

Hernia

In the case of 350 patients operated on from 1983 to 1986 we noted the presence or absence of an inguinal hernia. A hernia was recorded as present in 22.6% (79 patients) and absent in 34.6% (121). No record concerning hernia was made in 42.8% (150 patients).

Position

The position of the testis at operation is shown in the Table. A bewildering variety of terms was used to describe positions and those encountered most commonly are listed in anatomically descending fashion together with our terms of classification.

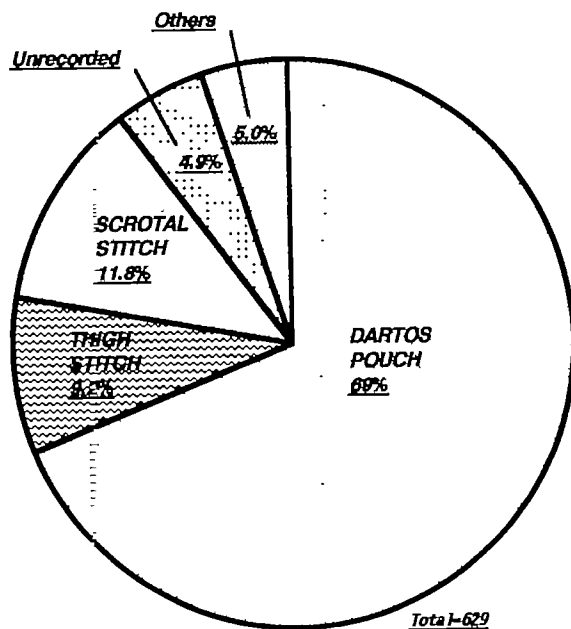


Fig. 4 Types of operation shown as percentage of total (629).

Table Position of Testis at Operation and ADR Classification

Level	%	ADR classification
Anorchia/agenesis	0.6	A ₀
Intra-abdominal	2.0	A ₁
Canalicular/inguinal ring	9.3	A ₂
Emergent/external ring	7.5	A ₃
Inguinoscrotal	2.4	A ₄
Subcutaneous/superficial		
inguinal pouch	58.1	D ₁
Ectopic	1.3	D ₂
Retractable	0.3	R
Unrecorded	18.4	U

Intra-abdominal (A₀, A₁)

Eighteen testes (2.6%) were not found outside the deep inguinal ring at initial operation. The outcome in these patients was as follows. Seven testes were successfully placed in the scrotum and 1 fixed at the neck of the scrotum awaits a second-stage procedure. Four patients (aged 33, 28, 20 and 17 years) underwent orchiectomy. The results of histological examination were available in 3 cases and showed no malignancy. One patient had a successful orchiopexy on one side and is awaiting treatment on the other side. Three patients were referred outside the area. One was treated by long loop

orchiopexy, the other was assessed by ultrasound and was awaiting laparoscopy, and in the third case no further information was available. No testes could be found on laparotomy in one patient and the remaining patient is due for review in the coming year.

Reoperation

Further procedures were required in 19 testes because of bad positions resulting from earlier procedures. The exact position of these testes before reoperation is not known. The initial operations performed on these patients were dartos pouch (10), scrotal stitch (5), thigh stitch (3) and others (1). This distribution did not differ significantly from that of the entire group, showing no advantage of one procedure over another. No correlation was found with the presence of an inguinal hernia ($P = 0.074$). In this series, 19 failures represents a failure rate of 2.7%. In no case was atrophy of the testis recorded following the initial procedure.

Discussion

The number of UDT operations performed in this centre is increasing. The dramatic rise between 1980 and 1981 may be related to the appointment of an extra surgeon. The steady rise is probably related to the decreasing age at operation. Nevertheless, some workers have found the incidence of UDT to be increasing (Chilvers *et al.*, 1984). The distribution between right and left has varied from study to study. Snyder and Chaffin (1955) and Scorer (1964) found that only 10% of UDTs were bilateral. Other researchers found almost 25% to be bilateral (Gross and Jewett, 1956; Shapiro and Bodai, 1978) and these figures more closely match ours. The suggestion that a high percentage of bilateral UDTs reflects inclusion of retractile testes is not borne out by the findings in this study. As in other series, ours showed a predominance of right UDT in unilateral disease. No clear reason has been found for this, although Snyder and Chaffin (1955) suggest that it was due to the left descending before the right. Risk factors such as being first born, maternal exposure to oestrogens during pregnancy or a deficiency of gonadotrophic hormones should produce bilateral effects, and infants with genetic abnormality are generally noted to have bilateral disease. No information was available in this study regarding predisposing factors but chromosome studies on 4 patients (intra-abdominal testes) were normal. There may be a

familial basis for UDTs and an autosomal dominant inheritance with incomplete penetrance has been suggested (Cutner and Abel, 1988). In the present study there were some examples of familial clustering, with 3 boys in one family affected and one set of twins with both affected. It is important to screen the other twin in cases of UDT and other boys in the family (Cutner and Abel, 1988). These and other factors would be assessed more easily in a prospective study.

The mean age at operation (9.5 years) is high. However, the downward trend is significant and, if it continues, the rising proportion of those operated on under 5 years of age will also become significant. The 1986 figure which we observed (13.7%) compares poorly with the 32% between 1981 and 1983 reported by Cooper and Little (1985). Chilvers *et al.* (1986) reported 15% treated at 3 years or less, 32% by the age of 5 and 50% by 7 years.

We attempted to discover the reasons for the delay in operating on these boys. The analysis was rendered incomplete by the retrospective nature of the study but certain facts were apparent. The average waiting time from referral to consultation was approximately 4 weeks. Once operation was decided upon, the average waiting list time was about 6 weeks. The lack of specific information in the records made it impossible to calculate the average age at referral but the impression gained was that it was high. Many boys were referred from the schools' medical examination at about 7 years of age or older. Some had been referred but had not attended until several months and several recalls had elapsed. In some of these cases it was noted that the UDT had not previously been noted, but perhaps more surprisingly it was recorded on occasions that the condition had been noted by parents but no action had been taken. These facts highlight the need for education of parents and the importance of vigilance by family doctors and paediatricians when examining young boys.

A useful system has been used in this hospital since the closing years of the study period and it is responsible for the significant drop in age at operation. All boys are examined at birth or shortly after, before discharge, specifically for UDT. Those found to have absent testes are referred immediately to the surgical service and follow-up arranged. Many testes descend spontaneously in the first 3 months of life, but few thereafter. At this time retractility begins to increase with the development of the cremaster (Scorer, 1964). Confusion at this time is possible and may account for the high rates of orchiopexy and apparent increases in the

prevalence of UDT (John Radcliffe Group, 1960; Chilvers *et al.*, 1984). Once the testis has been observed in the scrotum at birth or subsequently we may be confident of its eventual return. While ascent of the testis has been described (Atwell, 1985; Robertson *et al.*, 1988), usually in association with a patent processus vaginalis, it appears to be uncommon. The significance regarding fertility is unclear. Reported cases have been treated by orchiopexy. Further study of this group is needed and will only be possible if the results of first-day examinations and follow-up are known.

The position of the testis at operation was not available in 18.4% of the case notes. As noted above, a wide variety of terms was used (Table), making strict comparison difficult. We feel that if a simple system of nomenclature were adopted, the recording of position would be easier and more consistent. It would aid audit, research and communication—the basis of learning in surgery. That such a system is needed has been stated by Beltran-Browne and Villegas-Alvarez (1988), but their system did not take into account ectopic or retractile testes. The system we used does do this. It can be kept simple or can be expanded to include more detail by the addition of a letter or figure denoting size such as "N" for normal, "S" for small, *etc.*, or the volume in ml. This system could be the basis of a more definitive classification for prospective use. The Table shows that only 2% of testes were intra-abdominal, but Campbell (1942) found 14.3% to be inside the internal ring. No reason can be found to explain this difference.

A hernia was noted in 22.6% of patients. Again it was difficult to obtain information retrospectively. Other series have shown 0.8 to 4.4% in the normal population (Wobbes *et al.*, 1980). Jones and Bagley (1979) found a hernia in all of their patients undergoing operation using a particular technique, but did not comment on the other patients in their series. Gross and Jewett (1956) found significant indirect inguinal hernias in 90% of true UDTs. It has been suggested that the presence of a hernia increases the malignancy risk by a factor of 2.9 (Morrison, 1976) and its presence increases operation time, but we could show no significant ill effect in terms of the need for reoperation.

Our figures show that 2.7% of operations were unsuccessful over a mean follow-up period of 6.5 years. Jones and Bagley (1979) had no failures at 1 year using their technique. No particular operation appears at fault in the present series.

The small proportion of impalpable (A_0 , A_1) testes in this series cannot be explained. Several of

these patients would have benefited from laparoscopy and this investigation is now an integral part of the management of impalpable testes. This poses the question of whether these patients should be managed in local units at all or whether they should be referred to regional units where laparoscopy and more sophisticated imaging techniques are available.

No testes have undergone malignant change, according to the information available, although we would expect only 0.5% of testes to have changed in this period of follow-up in any case. This raises the question of follow-up. It is apparent from our records that none was undertaken and to institute it now would be a mammoth task. The risk from carcinoma seems delayed in these patients (Martin and Menck, 1975) and perhaps follow-up should also be delayed. It is not certain that follow-up of any kind is warranted (Giwerzman *et al.*, 1987). What is clear is that it should be decided at the time of admission what will be done.

This study has shown the distribution of UDTs to be similar to that reported elsewhere. The mean age at operation is a cause for concern but the trends are encouraging, helped by direct referral from paediatricians. This should be standard practice in all units. The new system of recording testicular position is simple and could form the basis of a new classification to aid note keeping and facilitate communication between centres.

Two further studies are planned, one to follow up the cohort of patients already identified with regard to fertility, testicular size and possible malignancy, the other to study prospectively a 10-year cohort and obtain accurate information on referral patterns, family history, testicular position, operations and success rates.

References

- American Academy of Pediatrics (1975). The timing of elective surgery on the genitalia of male children with particular reference to undescended testes and hypospadias. *Pediatrics*, **56**, 479–483.
- Atwell, J. D. (1985). Ascent of the testis: fact or fiction. *Br. J. Urol.*, **57**, 474–477.
- Bell, A. (1974). Psychological implications of scrotal sac and testes for the male child. *Clin. Pediatr.*, **13**, 838–847.
- Beltran-Browne, F. and Villegas-Alvarez, F. (1988). Clinical classification for undescended testes: experience with 1010 orchidopexies. *J. Pediatr. Surg.*, **23**, 444–447.
- Campbell, H. E. (1942). Incidence of malignant growth of the undescended testis. *Arch. Surg.*, **44**, 353–369.
- Chilvers, C., Dudley, N. E. and Gough, M. H. (1986). Undescended testis: the effect of treatment on subsequent risk of subfertility and malignancy. *J. Pediatr. Surg.*, **21**, 697–701.

- Chlivers, C., Pike, M. C., Forman, D. *et al.* (1984). Apparent doubling of frequency of undescended testis in England and Wales in 1962-1981. *Lancet*, **2**, 330-332.
- Cooper, B. J. and Little, T. M. (1985). Orchidopexy: theory and practice. *Br. Med. J.*, **291**, 706-707.
- Cunningham, J. H. (1921). New growths developing in undescended testicles. *J. Urol.*, **5**, 471.
- Cutner, A. and Abel, P. D. (1988). Undescended testis. a dual lesson. *Br. J. Urol.*, **62**, 273-274.
- Fonkalsrud, E. W. (1978). The undescended testis. *Curr. Probl. Surg.*, **15**, 1-56.
- Gehring, G. G., Rodriguez, F. R. and Woodhead, D. M. (1974). Malignant degeneration of cryptorchid testes following orchidopexy. *J. Urol.*, **112**, 354-356.
- Gilbert, J. B. and Hamilton, J. B. (1940). Studies in malignant testis tumors. III. Incidence and nature of tumors in ectopic testes. *Surg. Gynecol. Obstet.*, **71**, 731-743.
- Glwercman, A., Grinstead, J., Hansen, B. *et al.* (1987). Testicular cancer risk in boys with maldescended testes: a cohort study. *J. Urol.*, **138**, 1214-1216.
- Gross, R. E. and Jewett, T. C., Jr (1956). Surgical experiences from 1222 operations for undescended testes. *J.A.M.A.*, **160**, 634.
- John Radcliffe Hospital Cryptorchism Study Group (1986). Cryptorchism: an apparent substantial increase since 1960. *Br. Med. J.*, **293**, 1401-1404.
- Johnson, D. E., Woodhead, D. M., Pohl, D. R. *et al.* (1968). Cryptorchism and testicular tumorigenesis. *Surgery*, **63**, 919-922.
- Jones, P. F. and Bagley, F. H. (1979). An abdominal extraperitoneal approach for the difficult orchidopexy. *Br. J. Surg.*, **66**, 14-18.
- Karcher, G. (1967). Die Fertilität des behandelten pathologischen Hodenhockstandes unter besonderer Berücksichtigung des Zeitpunktes der hormonellen bzw. operativen Therapie. *Arch. Klin. Chir.*, **317**, 288.
- LeComte: Quoted by Johnson *et al.* (1968). Cryptorchism and testicular tumorigenesis. *Surgery*, **63**, 919-922.
- Martin, D. C. and Menck, H. R. (1975). The undescended testis: management after puberty. *J. Urol.*, **114**, 77-79.
- Mengel, W., Hienz, H. A., Sippe, W. G. *et al.* (1974). Studies on cryptorchidism: a comparison of histological findings in the germinative epithelium before and after the second year of life. *J. Pediatr. Surg.*, **9**, 445-450.
- Morrison, A. S. (1976). Cryptorchidism, hernia and cancer of the testis. *J. Natl. Cancer Inst.*, **56**, 731-733.
- Pike, M. C., Chlivers, C. and Peckham, M. J. (1986). Effect of age at orchidopexy on risk of testicular cancer. *Lancet*, **1**, 1246-1248.
- Robertson, J. F. R., Azmy, A. F. and Cochran, N. (1988). Assent to ascent of the testis. *Br. J. Urol.*, **61**, 146-147.
- Scorer, C. G. (1964). The descent of the testis. *Arch. Dis. Child.*, **39**, 605-609.
- Shapiro, S. R. and Bodal, B. I. (1978). Current concepts of the undescended testis. *Surg. Gynecol. Obstet.*, **147**, 617-625.
- Snyder, W. H., Jr and Chaffin, L. (1955). Surgical management of the undescended testis. *J.A.M.A.*, **157**, 129.
- Wobbes, T. H., Schraffordt-Koops, H. and Oldhoff, J. (1980). The relation between testicular tumors, undescended testes, and inguinal hernias. *J. Surg. Oncol.*, **14**, 45-51.

The Authors

M. V. McKiernan, FRCSE, FRCSI, formerly Registrar, Department of Surgery, Castlebar General Hospital. Now Registrar, Department of Plastic Surgery, Galway.
 P. D. Murphy, MSc, FRCSI, Consultant Surgeon.
 J. G. Johnston, FRCSE, FRCSI, Consultant Surgeon.

Requests for reprints to: J. G. Johnston, Department of Surgery, Castlebar General Hospital, Castlebar, County Mayo, Ireland.

Surgical Outcome of Orchiopexy. I. Previously Unoperated Testes

K. C. SAW, I. EARDLEY, M. J. S. DENNIS and R. H. WHITAKER

Department of Urology, Addenbrooke's Hospital, Cambridge

Summary—A total of 1209 undescended testes in 961 boys who had had no previous surgery for this problem have been reviewed with particular regard to the outcome of surgery in relation to the pre-operative and intra-operative assessment of the position of the testis. A third of impalpable testes were found at operation in the abdomen, a third in the inguinal canal and a quarter in the superficial inguinal pouch; 1% of all testes and 7% of impalpable testes were absent; 96% of all testes reached the scrotum at operation and this figure included 69% of abdominal and 94% of canalicular testes. In all 24 testes were excised—7 of which were abdominal, 8 canalicular and 9 were in the superficial inguinal pouch. The generalisation that the higher the undescended testis before operation the poorer the result, does not always hold true.

When advising parents or patients about the likely outcome of an operation for undescended testis it is sometimes difficult to give an accurate prognosis. In general, the higher the testis prior to operation the less satisfactory the result. However, there are exceptions to this generalisation. On occasions an intra-abdominal testis can be placed well into the scrotum whilst, conversely, some easily palpable testes appear to have little cord length.

The purpose of this report was to explore the association between the pre-operative and intra-operative positions of the undescended testis in relation to the final cosmetic and functional outcome. The study was made possible by the use of a consistent classification of undescended testis and by the keeping of careful records and illustrations in the patient's notes over a large number of years.

Patients and Methods

The names of 1247 boys operated on for undescended testes in the Department of Urology at Addenbrooke's Hospital during the period 1973–1990 inclusive were collected from operating department records. The notes of 1239 patients were

available for review, revealing 1591 undescended testes that had undergone operative treatment.

The review was limited to boys aged 16 years or under, who were under the care of the senior author (R.H.W.). These 1063 patients with 1346 undescended testes could be separated into 3 referral groups:

1. Those without any previous inguinal surgery to the undescended testes (961 boys, 1209 testes).
2. Those who had already undergone orchiopexy elsewhere (79 boys, 99 testes).
3. Those who had undergone previous ipsilateral inguinal surgery which had resulted in a "trapped testis" (37 boys, 38 testes).

Fourteen boys are included in both groups 1 and 2 as they were referred for treatment of a previously unoperated undescended testis, but were found to have a poor result from orchiopexy carried out elsewhere on the contralateral side.

Groups 2 and 3 are the subject of a separate study.

The lowest position attained after manipulation at the pre-operative clinical assessment was noted. In almost all cases this had been recorded diagrammatically in the notes. This pre-operative position was classified as being impalpable, palpable in the groin or palpable higher than normal in the scrotum.

In all boys a standard operative technique was used (Spitz, 1984), with special care being taken to divide the cremasteric fibres, to isolate and ligate any patent processus vaginalis and to divide any lateral fibres at the internal ring. For testes not found by standard exploration, the lower retroperitoneum and peritoneum were explored through an extended inguinal incision. The position of the testis when it was initially exposed at operation was recorded using the classification in the Table (Whitaker, 1992), with the exception that emergent testes were grouped with superficial inguinal pouch testes for simplification of the presentation of these data. The position after maximal length had been obtained by operation was also noted, as was the presence and size of any patent processus vaginalis (PPV). The post-operative result at routine follow-up (usually 6 weeks) was recorded, usually in the form of a diagram.

Results

As previously stated, the results in this report are confined to 961 boys (1209 testes) who presented with a previously unoperated undescended testis.

Age at operation

During the period under review the median age at the time of surgery fell. This is illustrated in Figure

Table Classification of Undescent

Impalpable	True position determined at operation as either absent, canalicular or abdominal.
Palpable	Emergent: just outside the external inguinal ring Superficial inguinal pouch: but can be manipulated into the neck of the scrotum High/mid scrotal Ectopic: thigh, base of penis, perineum or superficial inguinal pouch but cannot be manipulated into the neck of the scrotum

1, where it can be seen that during the last decade of the study the median age at operation fell from 7.6 (1981) to 4.9 years (1990).

Pre-operative findings

The pre-operative positions after manipulation were as follows: 703 testes (59%) were high scrotal, 356 (30%) were in the groin, whilst 134 (11%) were impalpable. The pre-operative position was not stated for 16 testes. The vast majority of those testes which were palpable in the groin were within the superficial inguinal pouch. There were 384 (40%) right-sided undescended testes, 304 (32%) left-sided and 273 (28%) bilateral.

Grade of surgeon

The senior author operated upon 659 testes (54.5%). The senior urological registrar operated on 230

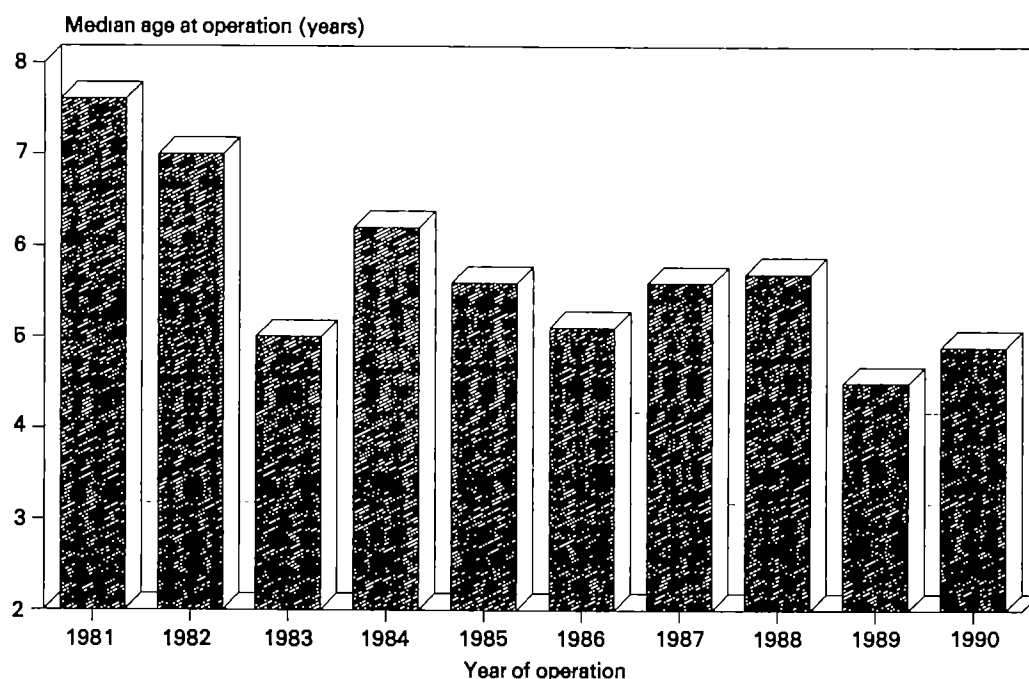
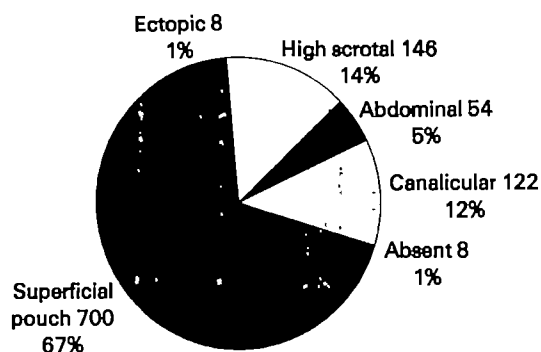


Fig. 1 Median age in years at operation, 1981–1990 inclusive.



In 171/1209 testes the operative position was not recorded

Fig. 2 Positions of 1038 testes at operation. In Figures 2 to 5 the numbers quoted are accurate, while the percentages have been calculated to the nearest whole number, by computer software. As a result, the total percentages for each pie chart lie in the range 98%–101%.

testes (19%) and the remaining 320 testes (26.5%) were operated upon by registrars or senior house officers under supervision.

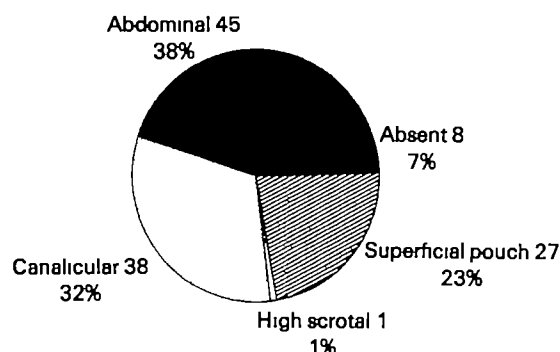
Operative findings

The positions of the testis at operation are shown in Figure 2.

The correlation between the pre-operative position and the position at operation is shown in Figures 3A–C. Approximately a third of impalpable testes were abdominal and a third canalicular. Just under a quarter were found in the superficial inguinal pouch.

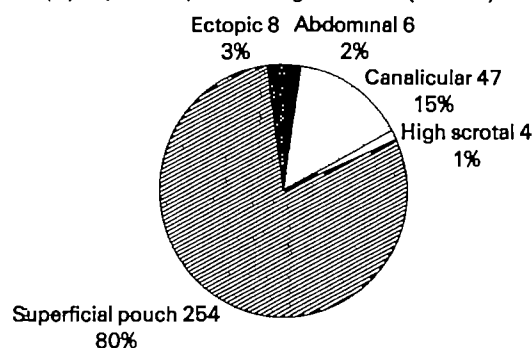
Approximately 1% of all undescended testes were absent and 7% of impalpable testes were absent. The vast majority of testes palpable in the groin and high in the scrotum were found in the superficial inguinal pouch.

(A) Operative position of impalpable testes (n = 119)



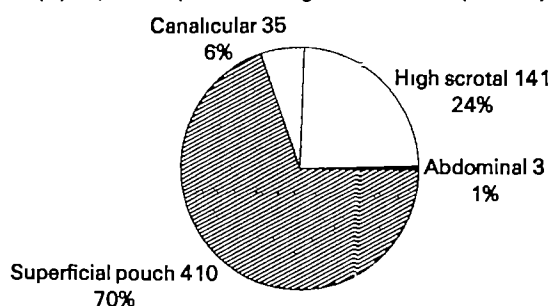
In 15/134 testes the operative position was not recorded

(B) Operative position of groin testes (n = 319)



In 37/356 testes the operative position was not recorded

(C) Operative position of high scrotal testes (n = 589)



In 114/703 testes the operative position was not recorded.

Fig. 3 Correlation between pre-operative position and position at operation.

Post-operative results

At the end of operation the positions of the testes were as follows: 1006 (83%) were at the bottom of the scrotum, 78 (6%) were in the middle and 81 (7%) at the top of the scrotum. Nine (1%) were in the groin and 32 (2.6%) were either absent or removed. Seven boys had a second operation performed by us. After a first operation that had resulted in 3 testes in the groin, 2 subsequently reached the top of the scrotum and 1 was removed. Of 4 testes at the top of the scrotum at the end of the first operation, 2 reached the bottom and 1 the middle of the scrotum. One was removed.

The correlation between the pre-operative position and the position at the end of all surgery is shown in Figures 4A and B. Approximately one-third of impalpable testes reached the bottom of the scrotum and a further fifth were absent or

removed. The majority of the 1057 palpable testes reached the bottom of the scrotum, although 5 boys underwent an orchiectomy.

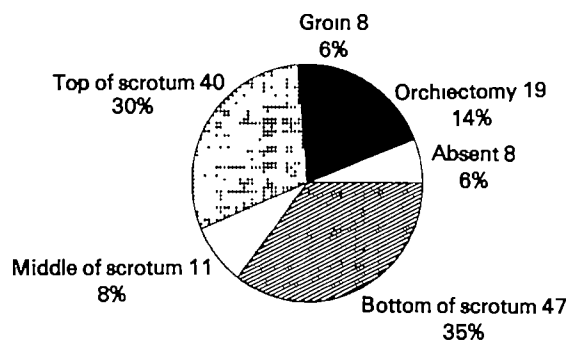
The results of operation for abdominal and canalicular testes are shown in Figures 5A and B; 70% of abdominal and 94% of canalicular testes eventually reached the scrotum.

Of the 700 testes found initially in the superficial inguinal pouch at operation only 9 failed to reach the scrotum and these were all excised. Of the 146 high scrotal testes 6 failed to reach the bottom of the scrotum for reasons which were not always clear in the operative notes.

Presence of hernia sac

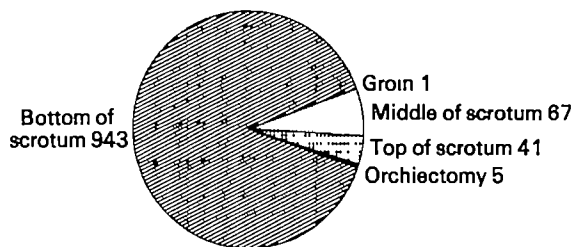
Pre-operatively 31 testes (2.6%) were associated with clinical evidence of a hydrocele and 39 testes (3.2%) were associated with a clinical hernia.

(A) Results of surgery in impalpable testes (n = 133)



In 1/134 testes the site at the end of surgery was not recorded

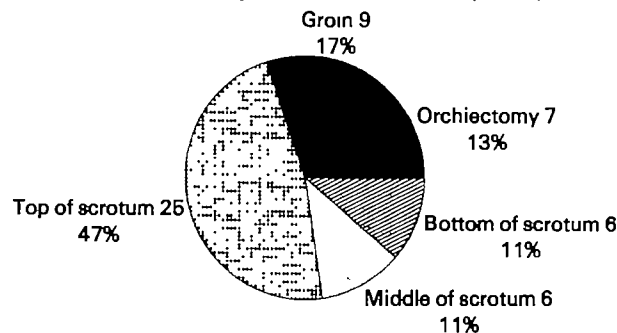
(B) Results of surgery in palpable testes (n = 1057)



In 2/1059 testes the position at the end of surgery was not recorded

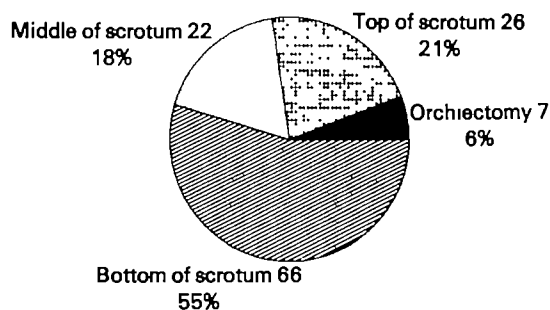
Fig. 4 Correlation between pre-operative position and position at end of all surgery

(A) Results of surgery in abdominal testes (n = 53)



In 1/54 testes the position at the end of surgery was not recorded

(B) Results of surgery in canalicular testes (n = 121)



In 1/122 testes the position at the end of surgery was not recorded

Fig. 5 Correlation between operative position and position at end of all surgery.

At operation 284 testes (23%) were found to be associated with a large PPV whilst 637 testes (53%) were associated with a moderate or small one. The presence (or absence) of a PPV was not recorded in 215 cases (18%) and in 73 testes (6%) it was noted that a PPV was not present.

Ascending testes

In this series 39 testes were associated with a history of ascent. In all cases there was documentation in the notes of a previously normal scrotal examination by a senior urologist or general surgeon. Many were noted at the time to be retractile testes. All were referred to us at a later date and all were confirmed as undescended.

At the pre-operative assessment all were palpable in the groin. At operation 3 were found to be canalicular, 19 were in the superficial inguinal pouch, 15 were high in the scrotum and in 2 cases the data were not recorded. In all cases an excellent result was obtained with good length and all testes reached the bottom of the scrotum. Clinically, none was felt to be associated with a hernia or hydrocele, but at operation 24 were found to have a PPV. In 3 cases no sac was seen and in the remaining 12 cases no record was made in the notes.

Discussion

We believe that this is the first study that has described from a large series of orchiopexies what can be expected from the operation in respect of the pre-operative and intra-operative findings. Good documentation with drawings of the pre- and post-operative positions made this review possible.

To date there has been no agreed classification of undescended testis and this has led to confusion when different series are compared. We feel that we have overcome this problem by describing the pre-operative findings as the best position of the testis after manipulation and by further defining the impalpable testis according to its position at operation (Whitaker, 1992).

No testicular atrophy was seen in this series when the patients were reviewed at 6 to 8 weeks and this may be a reflection of the respect we hold for this operation in this hospital. Three-quarters of boys were operated upon by a consultant or senior registrar and the rest by junior surgical staff under supervision.

Second operations for less than perfect first orchiopexies are not very successful in our hands when we have performed the first operation ourselves. The results of a second operation when

the first one was performed elsewhere will be discussed in a subsequent publication.

Some generalisations as to prognosis can be made from the results collated here. It was found that 7% of impalpable testes were absent and 43% of impalpable testes could be brought down to mid or low scrotum. In contrast, 8% of testes that were palpable in the groin pre-operatively could not be placed beyond the top of the scrotum by operation. For the whole group of previously unoperated undescended testes 96% reached the scrotum.

There was some inconsistency between the pre-operative position and the operative findings. For instance, 24% of impalpable testes were found in the superficial inguinal pouch whilst 7% of testes which had been palpable pre-operatively high in the scrotum were found at operation to be either in the inguinal canal or within the abdomen. These discrepancies might, in part, be attributed to excess mobility of the testis or to our occasional inability to feel a testis because of an excess of fat in the inguinal region in some of these children.

In conclusion, we believe that the operation of orchiopexy requires great care and should not be left to be performed by an unsupervised junior member of the surgical staff at the end of a busy operating list. A guarded prognosis should be given to the parents and patients and it is probably wise to mention that an orchiectomy is always a possibility even when the testis is palpable. The generalisation that high undescended testes give poorer operative results and *vice versa* should be used with caution, as there are many exceptions.

References

- Spitz, L. (1984). *A Colour Atlas of Surgery for Undescended Testis*. P 64. London: Wolfe Medical Publications.
- Whitaker, R. H. (1992). Undescended testis—the need for a standard classification. *Br J Urol*. 70, 1–6.

The Authors

- K. C. Saw, FRCS, formerly Registrar. Now Urology Registrar, Ipswich Hospital, Ipswich.
- I. Eardley, MChir, FRCS, Senior Registrar.
- M. J. S. Dennis, DM, FRCS, formerly Senior House Officer. Now Registrar, Department of Surgery, University Hospital, Nottingham.
- R. H. Whitaker, MD, MChir, FRCS, University Lecturer in Paediatric Urology, Department of Paediatrics, University of Cambridge; Honorary Consultant Urologist, Addenbrooke's Hospital, Cambridge.

Requests for reprints to: R. H. Whitaker, Department of Urology, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ

Case Reports

Occupational Urothelial Cancer in a Former Iron Foundry Worker

N. P. COHEN and D. M. THOMAS, *Department of Urology, Burton General Hospital, Burton-on-Trent*

The exposure of workers to urothelial carcinogens has been described in several industries (Case, 1966; The BAUS Subcommittee on Industrial Bladder Cancer, 1988). Workers in the iron industry have not been described as an at risk group. We report the case of an iron foundry worker who, as far as we know, has made the first successful claim for Prescribed Industrial Disease Benefit (PD C23).

Case Report

A 54-year-old former iron foundry metallurgist was referred with painless frank haematuria of recent onset. Urography and cystoscopy revealed 2 solid bladder tumours which were resected transurethrally. Microscopically these were poorly differentiated grade IV transitional cell carcinomas invading into muscle. Despite treatment with chemotherapy and radical radiotherapy tumour recurrence developed, and 1 year after initial presentation he underwent radical cystoprostatectomy with ileal conduit diversion. Histology revealed tumour invasion into the deeper muscle but there was no evidence of extravesical spread (pT3a). His post-operative recovery was satisfactory, although complicated by wound infection and delayed healing. He is impotent but otherwise well, with no sign of recurrence 34 months after cystectomy. He is the local branch secretary of the Urostomy Association.

He has no significant past medical history. However, between 1952 and 1972 he was employed in the iron industry to maintain the metallurgical specification of moulding sand. This is a mixture of silica sand to form the shape of the mould, and finely divided coal dust which acts as a reducing medium when ignited by hot metal to prevent the casting from fusing to the sand. When standing near the moulds he would inhale the products of coal dust combustion.

Whilst attending the Department of Health and Social Security office for sickness benefit he read the available leaflet on industrial diseases. He recognised that the exposure to coal combustion products he had received was similar to that suffered by workers in the coal gas and retort industries. He subsequently claimed for and

was awarded Industrial Injuries Disablement Benefit (PD C23).

Comment

Employees in gasworks and the coke retort industries have an increased risk of developing both lung and bladder cancer (Doll *et al.*, 1972). They were exposed to 2-naphthylamine in the fumes and coal-tar from coke ovens and retort houses. During the 1960s coal gas manufacture was phased out. However, there may be a number of industries where workers have received, and continue to receive, prolonged exposure to coal combustion products without adequate recognition of the risk. Apparently coal dust is used only in the iron industry, so this risk will not apply to workers in non-ferrous metal works or to those in the steel industry.

References

- Case, R. A. M. (1966). Tumours of the urinary tract as an occupational disease in several industries. *Ann. R. Coll. Surg. Engl.*, **39**, 213-235.
- Doll, R., Vessey, M. P., Beasley, R. W. R. *et al.* (1972). Mortality of gasworkers—final report of a prospective study. *Br. J. Ind. Med.*, **29**, 394-406.
- The BAUS Subcommittee on Industrial Bladder Cancer (1988). Occupational bladder cancer; a guide for clinicians. *Br. J. Urol.*, **61**, 183-191.

Requests for reprints to: N. P. Cohen, 38 Woodleigh Avenue, Harborne, Birmingham B17 0NJ.

Malignant Hypertension due to Embolisation of a Clear Cell Renal Carcinoma

C. S. J. PROBERT, D. E. OSBORN and E. M. WATKIN, *Department of Urology, Leicester General Hospital, Leicester*

A case is presented of malignant hypertension complicating therapeutic embolisation for renal carcinoma. Goldblatt hypertension complicating renal tumours has been described but not after embolisation. Clinicians should be aware of this previously unreported and potentially fatal complication of the procedure.

Case Report

A 63-year-old Jehovah's Witness presented with a 9-month history of frank haematuria. A right renal mass was palpable and blood pressure was 140/80 mmHg. Haemoglobin was 6.4 g/dl. Arteriography demonstrated a right renal tumour. She refused blood transfusion prior to surgery and so the kidney was embolised with Ivalon and Gianturco coils. One month later, haemoglobin was 8.8 g/dl and nephrectomy was postponed; blood pressure was 190/100 mmHg.

Two weeks later she was admitted with heart failure and headache. Blood pressure was 210/130 mmHg. Chest X-ray showed cardiomegaly, right pleural effusion and pulmonary oedema. Haemoglobin was 11.3 g/dl. The urine contained blood and protein. Urea and creatinine were normal. She was given oxygen, diamorphine, frusemide and antihypertensive medication. After 10 days hypertension and heart failure were controlled with frusemide 40 mg, amiloride 5 mg, nifedipine 20 mg *bid* and atenolol 100 mg. One week later she underwent nephrectomy. Histology confirmed a renal clear cell carcinoma, with areas of necrosis. Blood pressure fell post-operatively and the antihypertensive medication was reduced. After 2 months, blood pressure was 140/80 mmHg on nifedipine 10 mg *bid*.

Comment

The role of the kidney in the aetiology of hypertension has long been recognised. Goldblatt *et al.* (1934) showed the effect of renal artery ligation on blood pressure in dogs.

Renal embolisation has been used in patients with renal carcinoma as a pre-operative measure to facilitate nephrectomy, reduce operative blood loss and also as palliative treatment (Kauffmann *et al.*, 1989).

There was a clear relationship between embolisation and malignant hypertension in this patient, as in the Goldblatt model. Clinicians should be aware of the possible complication of renal tumour embolisation.

References

- Goldblatt, H., Lynch, J., Hansal, R. F. *et al.* (1934) Studies on experimental hypertension; production of persistent elevation of systolic blood pressure by means of renal ischemia. *J. Exp. Med.*, **59**, 347-379.
- Kauffmann, G. W., Richter, G. M., Rohrbach, R. *et al.* (1989). Prolonged survival following palliative renal tumour embolisation by capillary occlusion. *Cardiovasc. Intervent. Radiol.*, **12**, 22-28.

Requests for reprints to: C. S. J. Probert, Medical Registrar, Leicester General Hospital, Gwendolen Road, Leicester LE5 4PW.

Verrucous Carcinoma of the Bladder

A. E. GROENEVELD, *Department of Urology, University of Natal Medical School, Durban, South Africa*

Case Report

A 41-year-old African male complained of voiding pain and suprapubic discomfort for 2 weeks. There was no gross haematuria.

On examination he had a firm, apparently immobile suprapubic mass. The penis and scrotum were normal. Neither genital warts nor enlarged lymph nodes were found. The urine showed red blood cells but no bilharzial ova. *Escherichia coli* was cultured. Full blood count and renal function tests were normal.

Intravenous urography showed bilateral hydronephrosis and hydroureter. There was marked tortuosity in both ureters. The bladder showed a large filling defect. Bimanual examination under anaesthesia suggested advanced bladder cancer.

At cystoscopy a necrotic mass was found originating from the anterior wall and dome of the bladder, resembling squamous cell carcinoma. The bladder capacity was 80 ml. Biopsies contained only necrotic material. A CT scan confirmed a large bladder tumour but showed no lymph node metastases.

Cystectomy and cutaneous ureterostomy were carried out. Recovery was uneventful and the patient was discharged on the twelfth post-operative day. Five months later he was asymptomatic. A CT scan showed no sign of metastases.

Pathology

The specimen consisted of a thick walled bladder with a raised, warty tumour measuring 12 × 7 cm, originating in the dome. The inter-ureteric bar and the orifices were free. On cut section the tumour appeared to have a well defined deep margin around a whorl-shaped centre of grey tissue. At microscopy thickened hyperkeratotic squamous epithelium without atypicality was found throughout the tumour. Multiple elongated surface projections protruded into the muscle, almost reaching the serosal surface in one area. This phenomenon is described as "invagination" rather than true infiltration, which was not seen (Fig.). The tumour appeared to be a solitary lesion. Bilharzial ova were found throughout the bladder. The diagnosis of verrucous carcinoma was made.



Fig. Thickened hyperkeratotic squamous epithelium is seen with no atypicality. Multiple elongated projections protrude into the muscle. (H and E $\times 180$).

Comment

Verrucous carcinoma is regarded as a highly differentiated form of squamous cell carcinoma (Ackerman, 1948). As a bladder tumour however, it is much less common than the latter and less than 100 cases have been reported. Of the 615 new cases of bladder cancer seen at this centre in the last 10 years, 155 were squamous cell carcinoma but only one patient had verrucous carcinoma. Bilharzia is almost always coexistent with verrucous carcinoma of the bladder (El-Bolkainy *et al.*, 1981). The tumour shows relatively low grade malignant and metastatic potential. This was borne out in our patient by the fact that the tumour had reached a large size, causing long-standing bilateral ureteric obstruction, without involving the regional lymph nodes. An unequivocal diagnosis often requires deep biopsies of the tumour base and preferably a cystectomy specimen. The slowly progressive growth pattern causes most patients to seek medical attention at an advanced stage, when cystectomy is the only answer. Radiotherapy should be used with caution, for in some cases of verrucous carcinoma of the oral cavity it has caused anaplastic change leading to rapid deterioration and death (Kraus and Peres-Mesa, 1966).

References

- Ackerman, L. V. (1948). Verrucous carcinoma of the oral cavity. *Surgery*, **23**, 670–678.
 El-Bolkainy, M. N., Mokhtar, N. M., Ghoneim, M. A. *et al.* (1981). The impact of schistosomiasis on the pathology of bladder carcinoma. *Cancer*, **48**, 2643–2648.
 Kraus, F. T. and Peres-Mesa, C. (1966). Verrucous carcinoma: clinical and pathologic study of 105 cases involving oral cavity, larynx and genitalia. *Cancer*, **19**, 26–38.

Requests for reprints to: A. E. Groeneveld, Department of Urology, University of Natal Medical School, 719 Umbilo Road, Durban 4001, South Africa.

Late Metastasis from Ovarian Tumour. An Unusual Cause of Hydronephrosis

W. A. McCALLION, P. F. KEANE, B. G. WILSON and W. G. LOUGHRIDGE, *Department of Urology, Belfast City Hospital, Belfast*

Case Report

A 67-year-old woman presented with a 6-week history of left loin pain, frequency, dysuria and rigors. A right nephrectomy had been performed 40 years earlier for pyelonephritis and 27 years ago a hysterectomy had been performed for menorrhagia. Fourteen years ago she had a left oophorectomy for a clinically benign ovarian neoplasm which proved to be a granulosa cell tumour, Stage Ia. On admission she was afebrile, although she was tender in the left renal angle. There was no palpable abdominal mass. Intravenous urography revealed moderate hydronephrosis with displacement of the ureter. Computed tomography showed the ureter to be displaced by a soft tissue, para-aortic mass of mixed attenuation, measuring 6 $\times$ 7 cm (Fig.). Urinary vanillylmandelic acid was normal. At laparotomy an encapsulated mass was found in the retroperitoneum with the ureter stretched and displaced laterally. The mass was excised without spillage, preserving the ureter and its blood supply. Enlarged pre-aortic nodes adjacent to the mass were biopsied. No other intra-abdominal abnormality was detected. Histopathological examination revealed the mass to be a secondary deposit from a granulosa cell tumour of the ovary similar to the lesion excised 14 years previously. The lesion was completely excised and there was no evidence of lymphatic involvement. The patient made an uneventful post-operative recovery and no further treatment is planned.

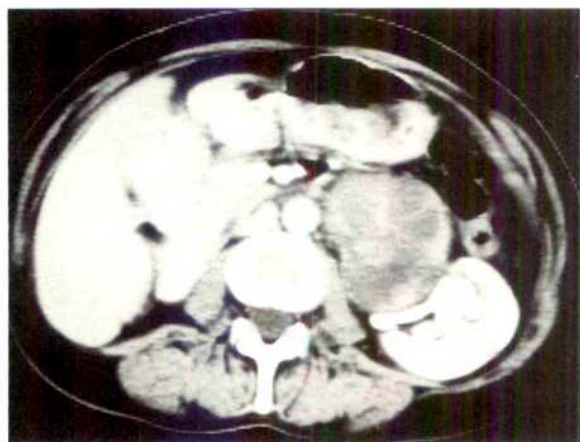


Fig. 1 CT scan showing retroperitoneal mass of mixed attenuation causing hydronephrosis.

Comment

This is the first case report in the literature of late retroperitoneal metastasis from a granulosa cell tumour presenting with hydronephrosis. Granulosa cell tumours (GCT) account for 1.2% of ovarian cancers; 90% are stage Ia and 5% are bilateral when diagnosed (Russell and Bannatyne, 1989). Histologically, granulosa cells are round or polyhedral, with pale cytoplasm forming large islands of cells. In 50% of cases degenerate tumour cells aggregate to form the characteristic Call-Exner bodies whose presence establishes the diagnosis. GCT occur most commonly in post-menopausal women in whom treatment is abdominal hysterectomy, bilateral oophorectomy and omentectomy. The contralateral ovary may be spared in pre-menopausal patients with early (Ia) disease. These tumours are moderately radiosensitive and adjuvant radiotherapy is indicated in advanced disease or if there has been tumour spillage (Lambert and Soutter, 1989). GCT are low grade malignancies and may recur up to 20 years after the initial diagnosis, usually within the peritoneal cavity. Retroperitoneal and extra-abdominal metastases are rare. Of 118 GCT treated at the Mayo Clinic 18.6% recurred at a mean of 6 years and the longest interval to recurrence was 23 years. No retroperitoneal recurrence was seen in this series (Evans *et al.*, 1980). In diagnosing retroperitoneal tumours a history of previous ovarian surgery is always significant and GCT in particular are associated with late recurrence and good long-term survival.

References

- Evans, A. T., Gaffey, T. A., Malkasian, G. D. *et al.* (1980). Clinicopathologic review of 118 granulosa and 82 theca cell tumors. *Obstet. Gynecol.*, **55**, 231–238.
- Lambert, H. E. and Soutter, W. P. (1989). Ovary, vulva and vagina. In *Treatment of Cancer*, ed. Sikora, K. and Halnan, K. Pp. 549–578. London: Chapman and Hall.
- Russell, P. and Bannatyne, P. (1989). Granulosa cell tumours. In *Surgical Pathology of the Ovaries*, ed. Russell, P. and Bannatyne, P. Pp. 316–332. London: Churchill Livingstone.

Requests for reprints to: P. F. Keane, Department of Urology, Belfast City Hospital, Belfast BT9 7AB.

Columnar Metaplasia Complicating Neurogenic Bladder in a Child

G. G. YOUNGSON, R. GALLEY and P. W. JOHNSTON,
Departments of Paediatric Surgery and Pathology, Royal
Aberdeen Children's Hospital, Aberdeen

Case Report

A newborn female presented at birth with sacrococcygeal teratoma (Fig. 1). Resection of the tumour (15 × 12 × 5 cm) resulted in progressive upper urinary tract dilatation consequent to denervation of the bladder. Diversion of the upper urinary tract was effected 7 months later by transuretero-ureteric anastomosis and a ureteric stoma. Subsequent reassessment at age 6 years documented continuing upper tract sepsis and declining renal function (isotope GFR = 37 ml/min/1.73 m²). Grade V vesicoureteric reflux was present. Undiversion was carried out and clean intermittent self-catheterisation introduced. Reimplantation of the ureters was performed but failed to control sepsis and deterioration of renal function continued, with current GFR 15 ml/min/1.73 m² at age 12.

A heavy and troublesome proteinaceous deposit developed coincident with the introduction of growth hormone into her management. Cystoscopy and random bladder mucosal biopsy were carried out in preparation for renal transplantation, in an attempt to characterise the deposit and locate its source. The biopsy was a mucosa-covered fragment, 6 × 3 mm. Sections showed generalised columnar metaplasia of the surface epithelium (Fig. 2) which stained positively for mucins with periodic acid Schiff after diastase, alcian blue (pH 1.5, 2.5) and high iron diamine alcian blue. The lamina propria was mildly and superficially inflamed. Whilst the macroscopic features were those of neurogenic bladder, the biopsy demonstrated columnar metaplasia as the source of the urinary mucin.



Fig. 1 Extensive sacrococcygeal teratoma undergoing spontaneous necrosis.

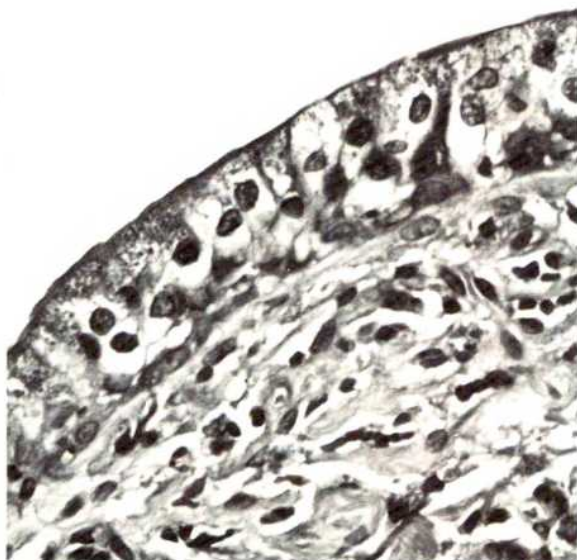


Fig. 2 Bladder mucosa from patient at 12 years of age, showing mucous metaplasia of the epithelium. There is a sparse inflammatory infiltrate, comprising mainly lymphocytes and some plasma cells, in the lamina propria (H and E $\times 450$).

Comment

Intestinal epithelium in the urinary tract has been reproduced experimentally in response to *Escherichia coli* infection and has previously been considered a metaplastic process determined by the endodermal origin of the greater part of the bladder (Gordon, 1963). The staining pattern of the mucins is consistent with epithelium of intestinal type. Similar changes in the upper urinary tract have been found in response to calculi (Salm, 1969) and an association with bladder adenocarcinoma has been identified (Young and Parkenhurst, 1984). This latter finding influences the management of this child, which is proposed as transplantation into an ileal loop with subsequent native nephroureterectomy and staged undiversion by ileocystoplasty if reversion to transitional epithelium occurs in the bladder. Pre-emptive cystectomy will be performed should the mucinous metaplasia persist.

The combination of chronic sepsis and supravescical diversion have previously been causally associated with columnar metaplasia of the urinary bladder (Young and Parkenhurst, 1984) and both apply to our patient. We would therefore recommend early biopsy of the bladder in cases of mucinous urinary deposit to allow early diagnosis of columnar metaplasia development and an appropriate management strategy in these rare cases.

References

- Gordon, A. (1963). Intestinal metaplasia of the urinary tract epithelium. *J. Pathol. Bact.*, **85**, 441–444.
- Salm, R. (1969). Combined intestinal and squamous metaplasia of the renal pelvis. *J. Clin. Pathol.*, **22**, 187–191.
- Young, R. H. and Parkenhurst, E. C. (1984). Mucinous adenocarcinoma of bladder. Case associated with extensive intestinal metaplasia of urothelium in patient with nonfunctioning bladder for twelve years. *Urology*, **24**, 192–195.

Requests for reprints to: G. G. Youngson, Department of Surgery, Royal Aberdeen Children's Hospital, Cornhill Road, Aberdeen AB9 2TG.

Syphilis of the Ureter

D. J. WARWICK and S. C. W. HARRISON, *Department of Urology, Southmead Hospital, Bristol*

Case Report

A 71-year-old man presented with a short history of colicky loin pain and haematuria. Intravenous urography

and retrograde urography showed obstruction of the distal ureter. Urine cytology was repeatedly normal. A distal ureterectomy and Boari cystoplasty were performed.

Histology (Figs 1 and 2) revealed an inflammatory reaction typical of luetic disease with vascular intimal scarring and giant cells with cholesterol clefts.

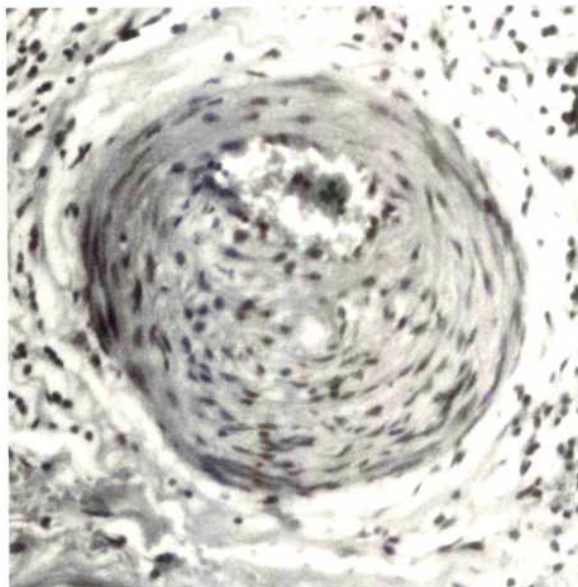


Fig. 1 Artery in ureteric lamina propria showing endarteritis obliterans. (H and E $\times 440$).

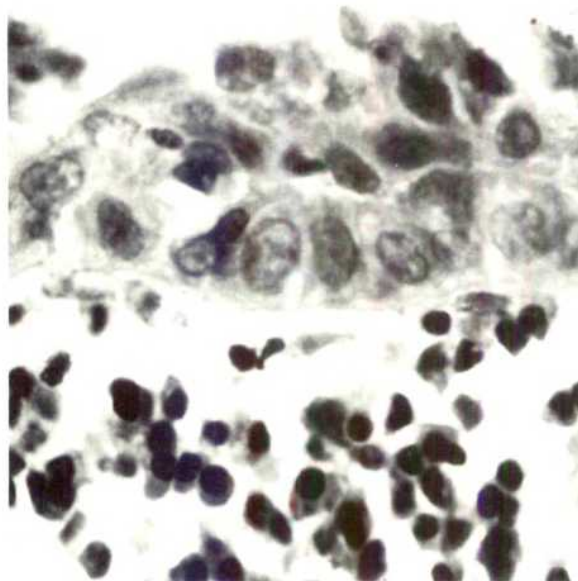


Fig. 2 Ureteric mucosa showing urothelial dysplasia and a florid inflammatory cell infiltrate in which plasma cells predominate. (H and E $\times 1750$).

The patients had a known history of syphilis. As a young seaman he had been treated on a number of occasions for venereal disease. He had recently seen an ophthalmologist for choroidal atrophy and heavy corpuscle pigmentation due to old spirochaetal infection. He was under review by a cardiologist for aortic incompetence. The TPHA test was positive (a sensitive indicator of previous spirochaetal infection), as was the FTA (a specific indicator of treponemal infection).

Comment

One third of patients with syphilis develop tertiary syphilis (Walter and Israel, 1987). Virtually any organ may be affected and the disease is a notorious mimic. Diagnosis can be challenging, since serological tests are not always positive and it is difficult to demonstrate the treponemes directly. Thus one often relies on indirect clinical and histological evidence.

A literature search has revealed no reported cases of syphilis affecting the ureter.

Acknowledgement

We thank Dr A. MacIver for providing photographs and histological advice.

Reference

Walter, J. B. and Israel, M. S. (1987). *General Pathology*. Pp. 271-274. Edinburgh: Churchill Livingstone.

Requests for reprints to: D. J. Warwick, 29 West Mall, Clifton, Bristol BS8 4BG.

Pontine Pathology and Voiding Dysfunction

C. D. BETTS, R. KAPOOR and C. J. FOWLER, *Department of Uro-Neurology, National Hospital for Neurology and Neurosurgery, London*

Case Report

A 34-year-old man presented with a history of delayed ejaculation, voiding difficulties and diplopia. His most troublesome symptom was profound difficulty in initiating voiding, despite an apparently normal desire to void. His symptoms had developed over a period of several weeks, 3 months before the referral. On 2 occasions catheterisation was required to relieve acute urinary

retention. Neurological examination revealed bilateral internuclear ophthalmoplegia and extensor plantar responses. Combined sphincter electromyography and urodynamic studies demonstrated a stable detrusor with a normal desire to void occurring at 850 ml. There was no detrusor sphincter dyssynergia and voiding occurred predominantly by abdominal straining (Fig. 1).

A magnetic resonance scan demonstrated a lesion involving the midbrain and upper pons (Fig. 2); imaging of the whole cord was normal. The lesion was biopsied stereotactically but unfortunately there were no specific features on which a diagnosis could be based, although there was no evidence of malignancy. The radiological appearances were consistent with a developmental abnormality such as a dermoid or teratoma. No urological cause for his voiding difficulties could be identified.

Comment

Barrington (1925) first recognised the importance of the pons in normal micturition, from animal studies. A spinobulbospinal pathway is thought to pass through a micturition centre in the pontine tegmentum and it is this centre which is thought to co-ordinate detrusor sphincter action during micturition. However, there have been remarkably few clinical reports to support the existence of a pontine

micturition centre in man. Ueki (1960) reported urinary symptoms in 22 adults with pontine tumours and Renier and Gabreels (1980) observed urinary retention in children with pontine tumours. The urinary symptoms reported in patients with pontine tumours have been urinary retention and difficulty in voiding. Supraspinal lesions are more often associated with frequency, urgency and incontinence. This case history provides further clinical evidence for the importance of the pons in micturition and suggests that the centre may lie in the upper dorsal tegmentum.

References

- Barrington, F. J. F. (1925). The effect of lesions of the hind and midbrain on micturition in the cat. *Quart. J. Exp. Physiol.*, **15**, 81–102.
- Renier, W. O. and Gabreels, F. J. M. (1980). Evaluation of diagnosis and non-surgical therapy in 24 children with a pontine tumour. *Neuropediatrics*, **11**, 262–271.
- Ueki, K. (1960). Disturbances of micturition observed in some patients with brain tumour. *Neurologia Med. Chir.*, **2**, 25–33.

Requests for reprints to: C. D. Betts, Uro-Neurology Unit, National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG.

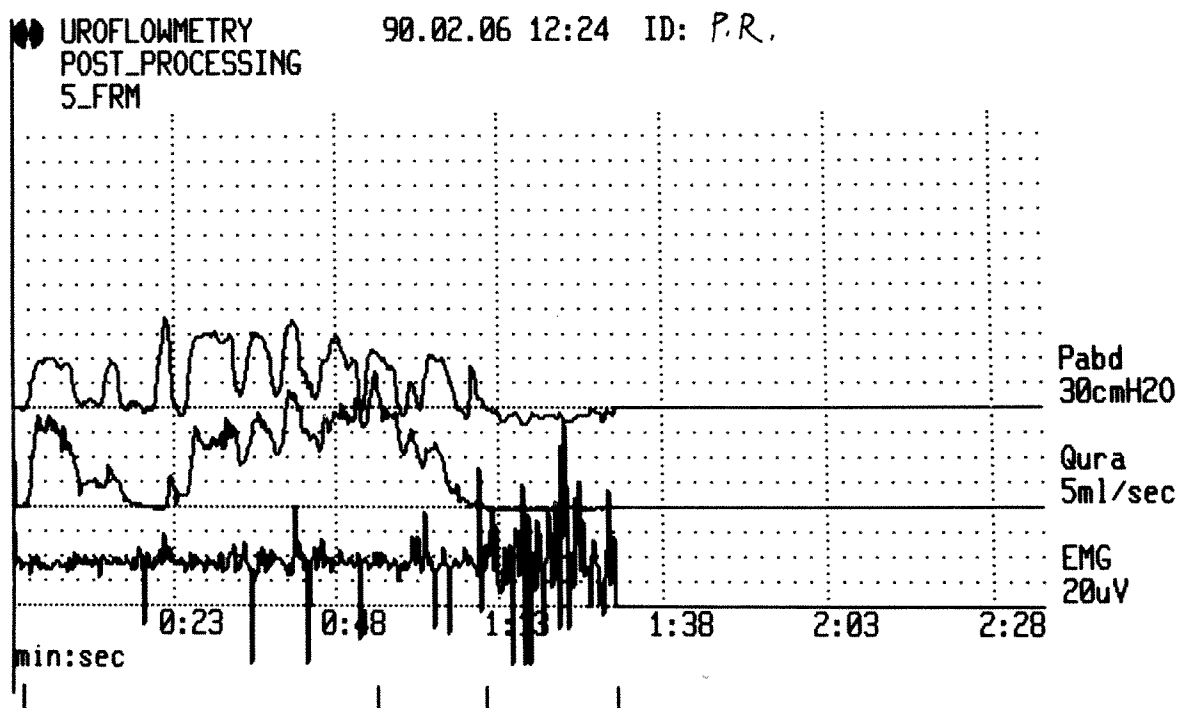


Fig. 1 Combined sphincter EMG and voiding urodynamic study demonstrating abdominal straining but no detrusor sphincter dyssynergia.

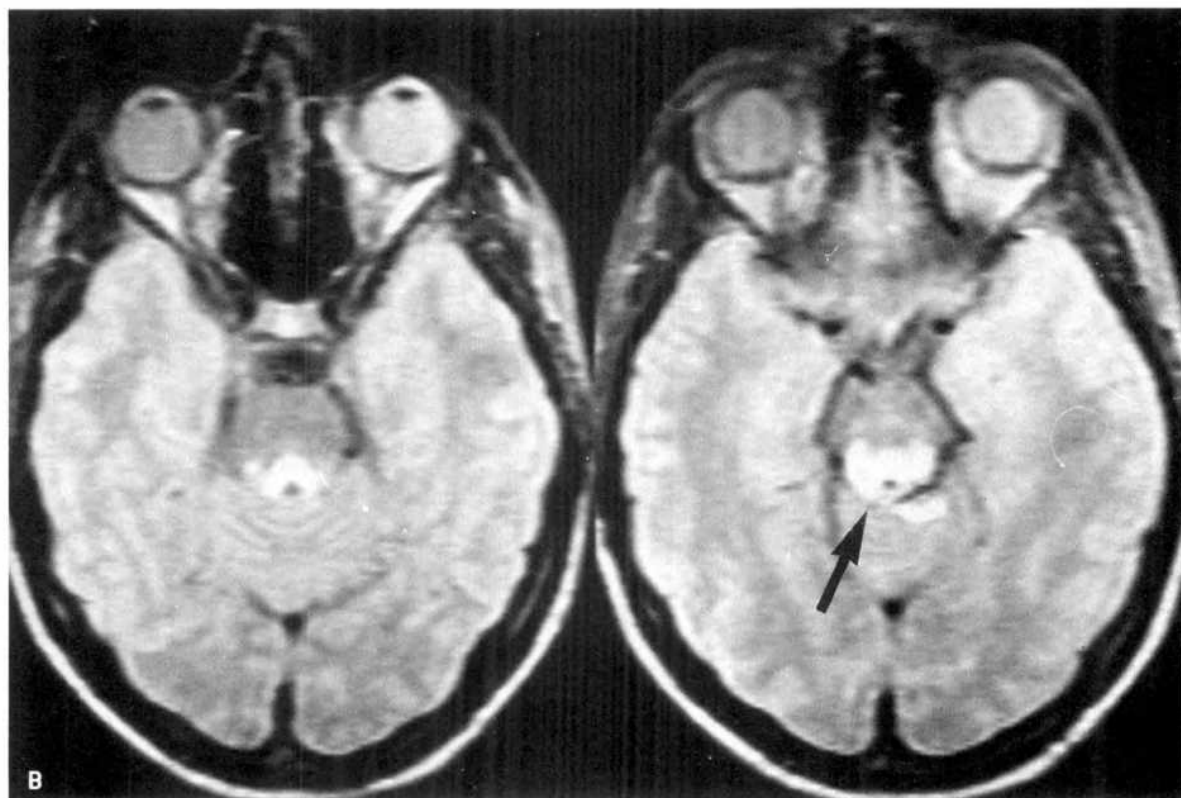
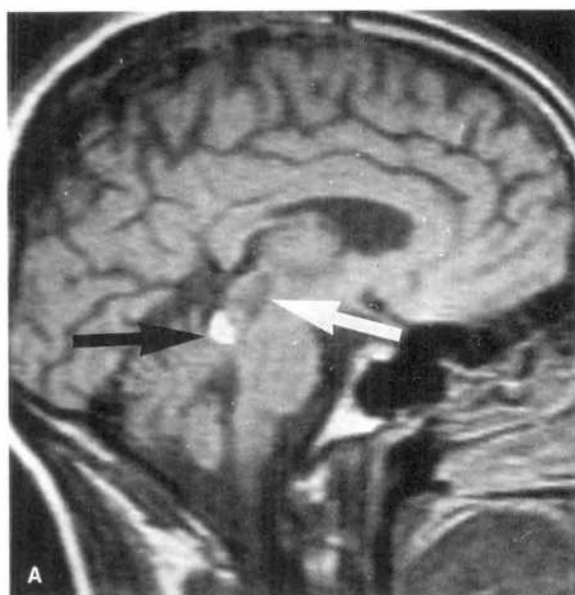


Fig. 2 Magnetic resonance image, moderately T2 weighted. (A) Sagittal view shows a low signal region predominantly in the midbrain (black arrow) and an associated high signal region (white arrow), likely to be fat. (B) The bilateral nature of the lesion is seen on the transverse view.

Metastatic Carcinoid Tumour Involving the Prostate

N. J. PARR, K. M. GRIGOR and A. W. S. RITCHIE,
University Departments of Urology and Pathology, Royal
Infirmary, Edinburgh

Case Report

A 68-year-old man presented with acute urinary retention. For approximately 2 years prior to this he had experienced

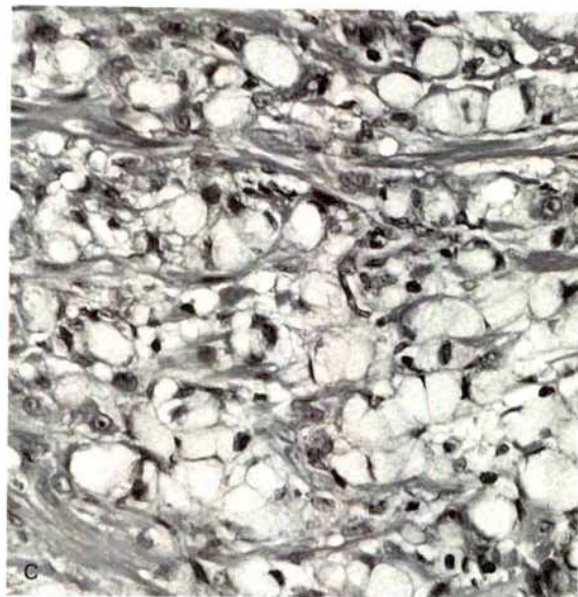
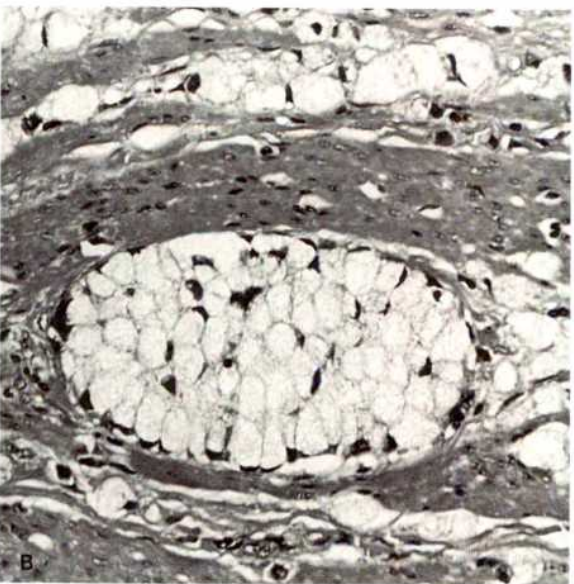
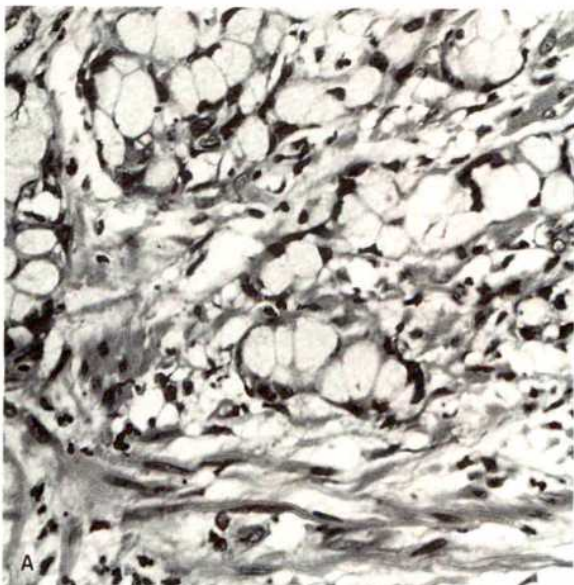


Fig. 1 (A) Appendix (1969). Clusters of carcinoid tumour with a goblet cell appearance are present, infiltrating the muscle wall of the appendix. (H and E $\times 320$). (B) Ileum (1984). The small bowel muscle is infiltrated by recurrent goblet cell carcinoid. Individual tumour cells and clusters are present. (H and E $\times 320$). (C) Prostate (1990). Goblet cell tumour similar to the previous carcinoid infiltrates the prostatic stroma. (H and E $\times 320$).

symptoms of outflow obstruction. Rectal examination revealed a moderately enlarged, smooth but firm prostate gland.

Twenty-one years previously he had undergone an appendectomy and histology revealed that the tip of the appendix contained goblet cell carcinoid tumour (Fig. 1A). Fifteen years after this a right hemicolectomy was performed for recurrent carcinoid tumour involving the terminal ileum and caecum (Fig. 1B) (Park *et al.*, 1990). Another small bowel resection was necessary 4 years later for further recurrent carcinoid and it had been impossible to excise the tumour completely on that occasion.

On this admission a transurethral resection of the prostate was performed and his initial recovery was unremarkable. However, 2 weeks post-operatively the patient developed intestinal obstruction requiring a laparotomy. This revealed widespread carcinoid throughout the right iliac fossa and a bypass procedure was carried out.

Microscopy of the prostate revealed extensive infiltration by tumour cells with a signet ring appearance (Fig. 1C). The cells stained negatively for prostatic specific antigen and for prostatic acid phosphatase. Their appearance was similar to that of the carcinoid tumour previously resected from the appendix and bowel (Figs. 1A and B).

Comment

Secondary tumours of the prostate are rare, accounting for approximately 1% of all tumours involving the gland (Johnson *et al.*, 1974). Malignant melanoma and bronchial carcinoma are the most frequent primary sources. The lesions may range from a few malignant cells in vascular channels to distinct nodules or widespread infiltration. Most are discovered incidentally at necroscopy in patients who have died of disseminated malignant disease. Occasionally, they may be diagnosed clinically, but in this situation they must be considered a late manifestation of malignant disease and usually herald a poor prognosis.

Secondary carcinoid tumour of the prostate has not previously been described, although it has recently been recognised that primary prostatic carcinoma may histologically mimic carcinoid (di Sant'Agnese, 1988). Some of these prostatic tumours exhibit neuroendocrine differentiation, demonstrable by silver staining techniques and immunocytochemistry. It is possible that such tumours arise from multipotent stem cells capable

of expressing more than one structural pattern. This is unlikely to be the origin of the carcinoid-like cells in the present case, since stains for exocrine prostatic specific markers were negative. Furthermore, the long history of extensive carcinoid in the bowel indicates that this was the primary site of the tumour.

Acknowledgements

The photomicrographs were taken by Mr J. Paul and we are also grateful for the assistance of Dr A. S. Krajewski.

References

- di Sant'Agnese, P. (1988). Neuroendocrine differentiation and prostatic carcinoma: the concept 'comes of age'. *Arch. Pathol. Lab. Med.*, **112**, 1097-1098.
- Johnson, D. E., Chabaud, R. and Ayala, A. G. (1974). Secondary tumors of the prostate. *J. Urol.*, **112**, 507-508.
- Park, K., Blessing, K., Kerr, K. *et al.* (1990). Goblet cell carcinoid of the appendix (Patient 7). *Gut*, **31**, 322-324.

Requests for reprints to: N. J. Parr, Department of Urology, Western General Hospital, Edinburgh EH4 2XU.

Points of Technique

Use of the Lachrymal Duct Probe in Epididymal Aspiration

K. R. LOUGHLIN, *Division of Urology, Department of Surgery, Brigham and Women's Hospital, Boston, USA*

Recent work has made the possibility of human fertilisation using epididymal sperm a reality (Berger *et al.*, 1985; Temple-Smith *et al.*, 1985; Bustillo and Rajfer, 1986; Silber, 1988). However, the importance of avoiding contamination of the sperm with blood was emphasised by Silber *et al.* (1988). This can compromise the processing of the sperm sample and make subsequent fertilisation less likely. We describe a technique which facilitates the retrieval of epididymal sperm without blood contamination.

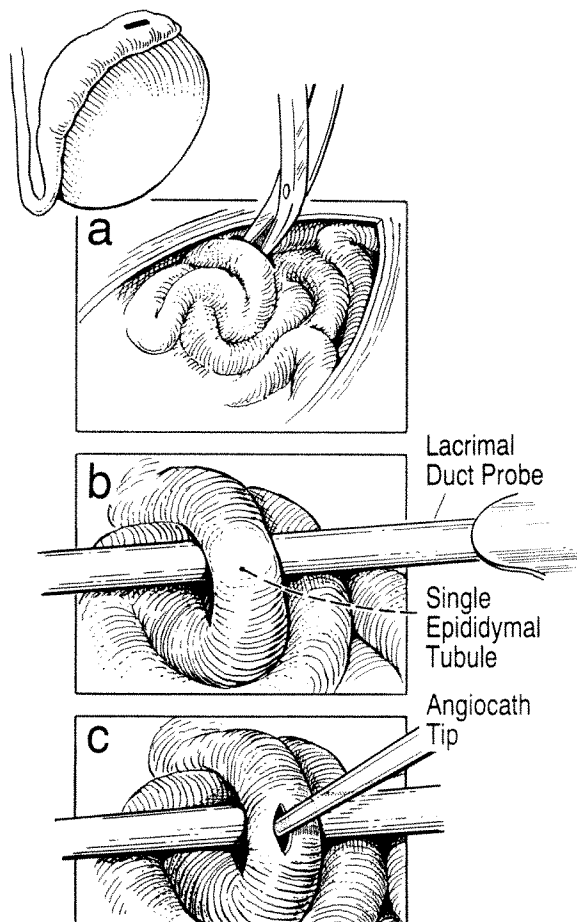
After the scrotum has been opened and the epididymis identified, a single epididymal tubule is dissected out with the microscissors under an operating microscope using a 10 to 40 $\times$ magnification.

Despite the routine use of microbipolar forceps, some bleeding is often encountered and can easily contaminate the sperm aspirate. A useful solution to this problem is the use of a lachrymal duct probe to elevate the selected epididymal tubule above any background bleeding and then to proceed with the sperm aspiration in the usual manner (Fig.).

References

- Berger, R. E., Muller, C., MacIntosh, R. *et al.* (1985). Operative recovery and insemination of vasal sperm: a new and repeatable procedure for treatment of the anejaculatory infertile male. *J. Urol.*, **133**, Abstract 195.
- Bustillo, N. and Rajfer, J. (1986). Pregnancy following insemination with sperm aspirated directly from vas deferens. *Fertil. Steril.*, **46**, 144–146.
- Silber, S. J. (1988). Pregnancy caused by sperm from vasa efferentia. *Fertil. Steril.*, **49**, 373–375.
- Silber, S. J., Balmaceda, J., Borrero, C. *et al.* (1988). Pregnancy with sperm aspiration from the proximal head of the epididymis: a new treatment for the congenital absence of the vas deferens. *Fertil. Steril.*, **50**, 525–528.
- Temple-Smith, P. D., Southwick, G. J., Yates, C. A. *et al.* (1985). Human pregnancy by *in vitro* fertilization (IVF) using sperm aspirated from the epididymis. *J. In Vitro Fert. Embryo Transfer*, **2**, 119–121.

Requests for reprints to: K. R. Loughlin, Division of Urology, Department of Surgery, Brigham and Women's Hospital, Boston, Massachusetts 02115, USA.



Laparoscopic Excision of an Intra-abdominal Testis

R. O. BECK, P. NICHOLL, N. C. HICKEY and J. BLACK,
Department of Surgery, Worcester Royal Infirmary, Worcester

Mini-laparotomy has previously been necessary to perform intra-abdominal orchiectomy for undescended testis in cases where orchidopexy is deemed unsuitable, for instance post-puberty. We describe a new minimally invasive technique using laparoscopy. The operation was performed in a 19-year-old man with an absent right testis confirmed by ultrasound to be lying at the internal inguinal ring. The left testis was normal.

Technique

With the patient fully anaesthetised a CO₂ pneumoperitoneum is produced in the routine fashion. A 10-mm cannula is inserted via a small stab incision at the umbilicus and the laparoscope with the camera attached placed through this port. The testis can now be visualised (Fig. 1). Two further cannulae are inserted under direct vision through the abdominal wall at such points as to give good access to the testis. It is then grasped and its mesentery placed under tension and cut with diathermy (Fig. 2). Once free it is removed through one of the 11-mm ports, all 3 of which are then closed with steristrips.

Comment

It is recommended that an intra-abdominal testis presenting in adult life be excised in view of the increased risk of malignancy and poor spermatogenic potential (Ford *et al.*, 1985), provided that the contralateral testis is normal. Until now this has involved an open operation. Localisation of undescended testes using laparoscopy has been

performed (Scott, 1982; Malone and Guiney, 1984) but we know of no reports describing the operation of laparoscopic intra-abdominal orchiectomy. The technique is straightforward, can be performed on a day-case basis and requires minimal post-operative convalescence.

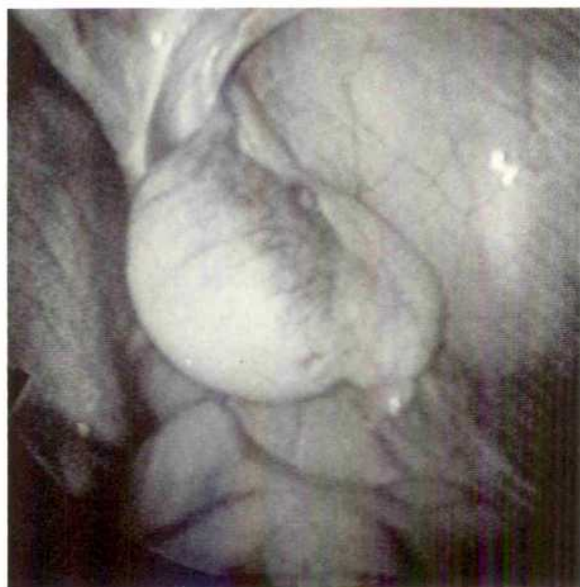
Acknowledgement

We are grateful for Mr G. Handy's help in setting up the laparoscopic surgery unit in Worcester.

References

- Ford, T. F., Parkinson, C. M. and Pryor, J. P. (1985). The undescended testis in adult life. *Br. J. Urol.*, **57**, 181–184.
- Malone, P. S. and Guiney, E. J. (1984). The value of laparoscopy in localising the impalpable undescended testis. *Br. J. Urol.*, **56**, 429–431.
- Scott, J. E. (1982). Laparoscopy as an aid in the diagnosis and management of the impalpable testis. *J. Pediatr. Surg.*, **17**, 14–16.

Requests for reprints to: R. O. Beck, Department of Uro-Neurology, The National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG.



Notices

William Cook Travelling Fellowship

In 1990, William Cook Europe Limited generously offered an annual sum of £3000 to finance a minimum of three travelling fellowships each year. Candidates must be members of the British Association of Urological Surgeons. Applications should be made to the Honorary Secretary of BAUS by 1 February, giving the following information: the name of the centre to be visited, the reason for the visit and an estimate of the cost of travel and accommodation. Prior agreement to the visit must be obtained from the surgeon/hospital in question.

Applications will be considered by a BAUS Committee. Successful applicants will be required to submit a report on the experience gained in the centre visited.

The Surgitek Prize

The Prize consists of a fully sponsored visit to the American Urological Association Annual Five-day Meeting, together with a tour of Surgitek's manufacturing facility in Racine, Wisconsin. It is open to trainees in urology and consultants who are within 5 years of first appointment. Entrants should submit a written paper, which may be on any subject, but must be unpublished, and must not have been submitted previously for the Surgitek Prize, or other prizes. The winning entry will be the one which is considered to be "The most significant contribution to urology".

Entries will be judged by three members of BAUS Council nominated at the October meeting of Council. Papers should be submitted in triplicate to the Honorary Secretary by 1 January each year.

Erratum

re Diuresis Renography. Recent Advances and Recommended Protocols. P. H. O'Reilly.

Br. J. Urol. (1992), 69, 113–120.

Throughout the section headed "Diuresis Renography—Interpretation", the expressions "SKGFR > 32 ml/min" and "SKGFR < 32 ml/min" should read "SKGFR > 16 ml/min" and "SKGFR < 16 ml/min" respectively. We apologise for this error.

Diary

1992

- August 2–5 International Society for Dynamics of the Upper Tract. Ninth Meeting. Akita, Japan. Contact: Dr B. L. R. A. Coolsaet, Klina Hospitals, Campus St Jozefziekenhuis, 2950 Kapellen, Antwerp, Belgium.
- August 7–9 Ninth Meeting of International Society for Dynamics of the Upper Urinary Tract. Akita, Japan. Contact: Dr Seigi Tsuchida, Department of Urology, Akita University School of Medicine, 1-1-1 Hondo, Akita, 010 Japan. FAX 81-188-36-2619.
- August 24–27 Edinburgh Urological Festival. Edinburgh. Contact: Urological Festival Secretary, University Department of Surgery (WGH), Western General Hospital, Edinburgh EH4 2XU.
- August 24–27 Third European Symposium on Uroradiology. Herlev, Denmark. Contact Dr H. S. Thomsen, Department of Diagnostic Radiology 54E2, Herlev Hospital, Herlev Ringvej 75, DK-2730 Herlev, Denmark.
- August 24–27 VIIth International Symposium on Urolithiasis and Related Clinical Research. Cairns, Australia. Contact: Dr Rosemary L. Ryall, Department of Surgery, Flinders Medical Centre, Bedford Park, South Australia 5042.
- August 30–
September 4 Ninth Congress of the International Pediatric Nephrology Association. Pediatric Urology Section. Jerusalem, Israel. Contact: Dr Amicur Farkas, Department of Urology, Shaare Zedek Medical Center, P.O.B. 3235, Jerusalem 91031, Israel.
- August 31 Workshop in Sacral Anterior Root Stimulation in Spinal Cord Injured Patients. Halifax, Nova Scotia, Canada. Satellite meeting of International Continence Society, September 1–4. Contact: Professor E. P. Arnold, Department of Urology, Christchurch Hospital, Christchurch, New Zealand.
- September 3–6 Tenth World Congress on Endourology and ESWL, Singapore. Contact: Secretariat, c/o Department of Urology, Singapore General Hospital, Outram Road, Singapore 0511.
- September 14–18 Fifth World Meeting on Impotence and Eighth Symposium on Corpus Cavernosum Revascularization, Milan, Italy. Contact: Organizing Secretariat, OMNIA Meeting and Congressi, Via Senato 18, 20121 Milan, Italy.
- September 15–18 Euro-American Conference on Urological Cancer—Clinical and Biological Progress. Athens, Greece. Contact: Erasmus Conference Centre, International Congress Organizers, 227–229 Kifissias Avenue, Athens 145 62, Greece.
- September 17–18 Seventh Annual Paediatric Urology Course. Selwyn College, Cambridge. Contact: Mr R. H. Whitaker, Department of Urology, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ.
- September 21–23 VIII Andrology Course. Barcelona, Spain. Contact: Secretaría General, Fundación Puigvert, c/. Cartagena 340–350, 08025 Barcelona, Spain. Tel: 34.3 2355614. Fax: 34.3 4559938.

- September 23–25 Polish Association of Urology Annual Meeting. Wroclaw, Poland. Contact: Organizing Committee, Katedra i Klinika Urologii, 50–043 Wroclaw, Pl. 1-Maja 8, Poland. Tel: 347-59. Fax: 254 101.
- October 1–2 Continuing Medical Education and Training in Europe: the Future. London. Contact: Dr M. W. N. Nicholls, Conference Office, c/o Fellowship of Postgraduate Medicine, 6 St Andrew's Place, London NW1 4LB. Tel: (44) (0)71 935 5556. Fax: (44) (0)71 224 3219.
- October 1–3 Annual Meeting of the Swiss Society of Urology. Leysin, Switzerland. Contact: Prof. Dr P. Graber, Clinique de Chirurgie Urologique, Hôpital cantonal, CH-1211 Genève 4, or Prof. Dr D. Hauri, Urologische Klinik, Universitätsspital, CH-8091 Zürich.
- October 1–3 Fourth World Congress of VideoUrology. Monte Carlo, Monaco. Contact: Convergences—VideoUrology '92, 120 Avenue Gambetta, 75020 Paris, France. Telex: 216 911 F. Fax: (33-1) 40 31 01 65.
- October 3 Meeting of the Belgian Association of Urology. Bruges, Belgium. "Early diagnosis and treatment of localized carcinoma of the prostate". Contact: Dr J. Ampe, Department of Urology, A.Z. St Jan, Ruddershove 10, 8000 Brugge, Belgium.
- October 7–11 1992 Duke Urologic Assembly. "Contemporary Issues in Urology". Pinehurst, North Carolina. Contact: Linda Mace, Assembly Coordinator, Box 3707, Duke Medical Center, Durham, NC 27710, USA.
- October 9–10 BAUS Autumn Meeting, Swansea. Contact BAUS Office.
- November 1–4 Third International Workshop on Carcinoma *in situ* and Cancer of the Testis. Copenhagen, Denmark. Contact: Workshop Secretariat, c/o Professor N. E. Skakkebaek, University Department of Growth and Reproduction, Section 5064. Rigshospitalet, 9 Blegdamsvej, DK-2100, Copenhagen, Denmark.
- November 8–10 Fourth International Conference of the Society for Minimally Invasive Therapy. Dublin, Ireland. Contact: Professor J. Fitzpatrick, 47 Eccles Street, Dublin 2, Ireland. Tel: +353-1-308530. Fax: +353-1-300345.
- November 27–28 International Postgraduate Course on Reconstructive Surgery of the Lower Urinary Tract in Children. Amsterdam, The Netherlands. Contact: Conference Secretariat, Bureau PAOG Amsterdam, Tafelbergweg 25, 1105 BC Amsterdam, The Netherlands: Tel: +31 20-566 4801. Fax: +31 20-696 3228.
- December 4–5 Eighth International Steglitz Paediatric Surgical Congress. Berlin, Germany. Contact: Dr F. Schier, Kinderchirurgie, Univ.-Klinikum Steglitz, Hindenburgdamm 30, 1000 Berlin 45, Germany. Tel: (030) 798 4181 or 798 2909; Fax: (030) 798 4141.
- 1993
- January 26–29 Ninth Copenhagen Symposium on Endoscopic Urological Surgery. Herlev, Denmark. Contact: Dr F. Rasmussen, Department of Urology, Herlev Hospital, DK-2730 Herlev, Denmark.
- March 19–20 Second European Congress on Ambulatory Surgery. Brussels, Belgium. Contact: Dr C. De Lathouwer, Brussels One Day Clinic, Avenue du Duc Jean 71–73, B-1080 Brussels, Belgium. Tel: +322/424.1212. Fax: +322/425.7076.

Book Reviews

Treatment Perspectives in Urologic Oncology.

Edited by R. D. Williams and P. R. Carroll. Pp. xii + 240. New York, Oxford, Beijing, Frankfurt, São Paulo, Sydney, Tokyo, Toronto: Pergamon Press. 1990. Price: £30.00; US\$47.50.

Urological oncology is undergoing rapid and fundamental change; there are new treatments, new investigations and new concepts of tumour biology which are likely to lead in the long term to the most radical changes in our ability to manage patients with cancer. The stated purpose of the book is to focus on several innovative approaches under investigation as treatment for urological cancer; there are 12 chapters on renal sparing surgery for renal cancer, monoclonal antibodies, adoptive immunotherapy, biological response modifiers, systemic chemotherapy, stage I testis teratoma, neutron treatment, stage A prostate cancer, fine needle biopsy, flow cytometry, intravesical chemotherapy, and incontinence and impotence after radical prostatectomy. The book is well produced and reasonably priced. It was published in 1990 and most chapters include references up to 1988 or 1989. While most of the contents are available in recent publications in journals, it is useful to have up-to-date reviews of these topics available in a single volume. The difficulty with any such book is the rapidly expanding nature of the field; already some chapters are not quite up-to-date and some are too speculative given the data available.

Although an enjoyable book to read, it does not have a well textured feel to it; perhaps because its intended audience had not been defined, the depth to which the several areas are covered varies widely. The chapter on monoclonal antibodies includes scanty and frankly unhelpful details of methodological aspects of preparation. It considers their potential uses but does not review chimeric or humanised monoclonal antibodies which will probably be critical to their effective clinical use. It was also a little disappointing that the authors from the National Cancer Institute did not update their results on IL-2 plus LAK cells for renal cancer first published 4 years ago (4 complete responses—11%). There is a useful review of the role of renal sparing surgery for renal cancer by Andrew Novick and the management of incontinence and impotence after radical prostatectomy from Peter Carroll and colleagues. The section on intravesical chemotherapy concludes that there have been few recent advances; whilst this may be the case, the subject deserves a more critical and thoughtful analysis than is provided. The chapter on stage A prostate cancer is well referenced. However, it is difficult to accept the authors' conclusion that repeat TURP is of use as a staging procedure, because the bulk of the literature suggests that there is a high false negative rate with this procedure, since some men with apparently small volume AI disease on TURP

have more extensive disease (demonstrated after radical prostatectomy) at sites which are not sampled by TURP. The chapter on particle treatment offers some interest for those who have followed the recent controversy over neutron treatment. It gives a more optimistic perspective than the British experience would seem to justify; this demonstrated a high rate of treatment-related complications and death plus a low response rate. Howard Scher gives a well written overview of the role of neoadjuvant therapy in invasive bladder cancer. The inclusion of a chapter on fine needle biopsy in a book supposed to be dealing with recent advances is presumably aimed at North American urologists, who have been slow in accepting this technique. The reasons for this are various but technique apart, the most important reason is the confidence felt by the urologist in the cytologist's interpretation of the data.

This is a book to browse through and is worth considering as an addition to a bookshelf or library. It is difficult to know for whom this book is intended. It does not aim to offer a comprehensive review of advances in urological oncology and as such it is difficult to recommend this book to the trainee or general urologist as an exclusive, up-to-date addition to the library because more comprehensive texts are available.

Handbook of Nephrology. By P. E. Gower. Pp. viii + 224. Oxford: Blackwell. 1991. Price: £14.95.

The declared aim of this volume is to act as an aid to decision-making in common clinical situations in adult patients with renal disease. Indeed the first edition, published in 1983, had the title "Nephrology Pocket Consultant". It certainly succeeds reasonably well in this objective and there is undoubtedly a need for this type of book in such a rapidly developing area of medicine. It is clearly and concisely written, with a large number of tables containing lists of factual information.

Perhaps inevitably, the coverage of individual topics is often superficial and one suspects that most doctors, faced with clinical uncertainty, will wish to refer to a more comprehensive text. On the other hand, a few topics of rather limited clinical importance, such as beta 2 microglobulin clearance and the tubular phosphate threshold, are dealt with in surprising detail. Some statements are repeated several times—for example, the fact that hyperuricaemia in chronic renal failure is not usually associated with gout. The author deliberately avoids discussion of controversial topics. The rather dogmatic approach to patient management which this involves is almost bound to give rise to dispute. Many nephrologists, for instance, would strongly disagree with the recommended daily intake of up to 90 ml of oral aluminium hydroxide in chronic renal failure, and the recommended use of intravenous salbutamol as first-line therapy for life-threatening hyperkalaemia. There is a tendency to raise complex topics, such as fractional

clearance measurements and renal autoregulation, without giving even a rudimentary explanation of them. One feels they would be best ignored. The overall standard of illustration is rather poor and some of the pictures, such as the one showing urinary red cells, are so unclear as to be of little use. There also seems to be an undue number of spelling and typographical errors, e.g. the description of angiotension connecting enzyme on page 68.

In summary, this book contains much useful information in an accessible form. It would have benefited from more ruthless pruning and from a higher standard of illustration.

Diagnostic Picture Tests in Urology. By N. J. R. George and P. Sambrook. Pp. 128. London: Wolfe Publishing. 1991. Price: £7.95.

This book enables both undergraduates and postgraduates to familiarise themselves with a wide range of common urological conditions, to test and perfect their diagnostic and therapeutic skills in urology, and to practise answering examination questions, including those that arise in clinical examinations. It achieves all of this with 195 illustrations, many coloured, of clinical and pathological conditions, X-rays, CT scans and instruments, each accompanied by between 2 and 5 questions of varying difficulty. The answers to the questions are printed at the end of the book.

The illustrations are of the very high quality we have come to expect of the publishers; together with the questions, they will entertain and even instruct trained urologists.

Controls of Sperm Motility: Biological and Clinical Aspects. Edited by C. Gagnon. Pp. 395. Boca Raton, Ann Arbor, Boston: CRC Press. 1990. Price: £78.00.

Defective sperm motility remains the most difficult problem both in male infertility in general and in *in vitro* fertilisation work in particular. Recent much publicised attempts to stimulate sperm activity *in vitro* with pentoxifylline, or to overcome the defect by zonal drilling techniques, have met with limited success. This is not surprising, since the basic biochemical and mechanical processes involved in sperm motility are complex and poorly understood. This book represents a comprehensive, scientifically based approach to understanding these mechanisms, what goes wrong with them, and how these faults may be corrected.

Thirty-two contributors have produced 16 chapters on biological aspects of control of sperm motility, and 6 chapters on clinical aspects. Ultrastructural assembly of the sperm tail, beating patterns, acquisition of motility during epididymal transit and interactions between

spermatozoal motility and constituents of the female genital tract are dealt with initially, and in great detail. Sperm chemotaxis and mode of action of egg peptides such as speract (secreted by the sea urchin egg and directly stimulating sperm activity) provide a fascinating insight into other worlds of reproduction. However, the biochemical sources of energy by which normal motility is maintained for hours or even days, and the bioenergetics of spermatozoa, are perhaps the most interesting and fundamentally important chapters providing the key to understanding the root causes of the failures that lead to recognisable poor sperm motility in clinical practice.

Clinical aspects are described well, with good descriptions of classical seminal analysis, antisperm antibody testing, computerised measurement of motility parameters and critical correlation with impairment of fertility. Capacitation and its importance prior to sperm-egg fusion is well documented. The influence of seminal plasma components on sperm motility is described by a team of scientists of whom the Editor is the senior author.

The urologist will turn for guidance to Hargreave's excellent chapter on clinical management and will not be disappointed—faults in collection of the specimen, live-dead staining and its relevance, poorly sustained motility and its relation to genital infection, immobilising antibodies and response to steroid therapy, and assessment of prognosis are all here. The final chapter is a gem—the effects of drugs, environmental and occupational toxins on sperm motility, often unrecognised and many reversible; this should be compulsory reading for all clinicians who take up the responsibility of looking after subfertile males.

Common Problems in Pediatric Urology. (Common Problems in Urology Series). Edited by E. T. Gonzales, Jr. and D. Roth. Pp. xviii + 485. St Louis, Baltimore, Boston, Chicago, London, Philadelphia, Sydney, Toronto: Mosby Year Book. 1991. Price: £53.50.

There seems to be a plethora of textbooks on urology being published at the moment, so that initial reaction to this book might be "Oh no, not another one!" It is, however, not just another one. It reads like an anthology of interesting short stories rather than a textbook on problems of paediatric urology.

In all, 47 topics are discussed by the authors, who come mainly from North America. None of the chapters is long but all are well written, to the point and have enough but not too many references. Most chapters begin with a hypothetical clinical problem being presented to the author, who then discusses relevant management. The whole range of paediatric urology is covered, with the emphasis on problems whose management is difficult or controversial. Thus Wilms' tumour is discussed in the context of bilateral disease, undescended testes in the context of the palpable testis, *etc.* Since each chapter

is short, all aspects of a problem cannot be dealt with in detail. The authors are well known in their field and concentrate on how they would manage the problem. This personal approach makes the book easy to read and more interesting than a routine textbook.

This book is presumably aimed at surgeons in training in paediatric and adult urology, but it will also be extremely useful for paediatricians. There is one annoying editorial error in Chapters 29 and 40, where the hypothetical problem has been placed in the wrong chapter. Otherwise this is an excellent book which can be strongly recommended and is good value for money.

Decision Making in Urology. Second edition. Edited by M. I. Resnick, A. A. Caldamore and J. P. Spirnak. Pp. xii + 250. Philadelphia, Hamilton: Decker. 1991. Price: £46.00.

Algorithms, ideally suited to the black and white issues of the computer or business world, rest less comfortably within the sphere of clinical medicine, where they attempt to bridge a gap between the generality of descriptive pathology and the specificity of individual disease. This problem is readily acknowledged by the editors, who point out that variants, alternative guidelines and exceptions to rules will need to be further researched from the references supplied. Decision trees are provided under the headings of symptoms, signs and therapeutic options for specific diseases.

Overall, the text takes a reasonable perspective of urological surgery, although inevitably some imbalance is to be found. Alan Wein condenses his writings on neurogenic bladder to one page, whilst the same amount of space is assigned to urethral diverticulum.

In general, algorithms work better when elaborating differential diagnoses rather than identifying therapeutic options, where the variable medical requirements of the individual patient are difficult to predict. A page on angiomyolipoma describes the diagnostic process well but is unable to define disease stability, risk of haemorrhage, frequency of follow-up CT or other factors which determine whether or not operation should be offered. A page on benign prostatic hyperplasia establishes the diagnosis but offers only limited operative guidelines for the very high percentage of elderly men who have this disorder.

The decision tree technique works best in circumstances where unusual or unexpected problems may occur and pages such as those on renal trauma and urinary leakage from the vagina ensure that the clinician considers all possibilities, although more complex subjects such as septic shock are difficult to cover in the available space.

This book does act as a valuable "aide memoire" and will direct the enquirer towards appropriate texts or original literature. The decision tree approach may not

suit all clinicians but it imposes a discipline and may thus find a useful place in the reference section of the departmental library.

Temperature and Environmental Effects on the Testis. (Advances in Experimental Medicine and Biology, Volume 286). Edited by A. W. Zorngiotti. Pp. xi + 335. New York, London: Plenum Press. 1991. Price: US\$85.00.

This book gathers together what is known about temperature regulation of the testis and the effects of altered temperature regulation on testicular function. It is the proceedings of a conference that took place in New York in 1989. As with any conference proceedings, there are good, bad and, in this case, sometimes obscure sections. For example, page 105 is a complete page of mathematical formulae concerning the analysis of validity of non-invasive intrascrotal temperature methods. One wonders whether mathematical precision can ever be appropriate given the relative crudity of the measuring techniques! Nevertheless, there is a wealth of information on testicular temperature in this book and it will be a reference source for researchers in this subject. It is unlikely to be of use to many urologists unless they have a research interest in this topic.

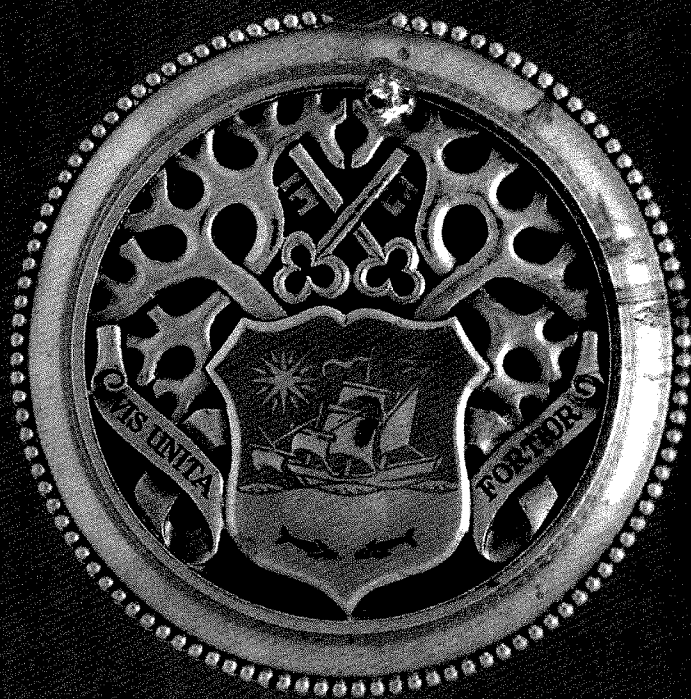
Operative Urology. Edited by F. F. Marshall. Pp. xxi + 631. Philadelphia, London, Toronto, Montreal, Sydney, Tokyo: Saunders. 1991. Price: £74.00; US\$125.00.

This book aims to give an up-to-date account of urological surgery: as the editor in his preface says, "more than half of what I do now did not exist when I completed my urology residency". Thus the need for a fresh look at urological techniques is ever with us. The text encompasses adult and paediatric urology. There is also a section on endoscopy and extracorporeal shock wave lithotripsy. Endoscopy for transurethral resection of bladder tumours is included under out-patient surgery, as indeed are a number of other procedures that have not yet become out-patient items in many countries outside the USA.

The text is marred by a number of indifferent illustrations, some unhelpful operative photographs and some figures that are either too large or too small. Most multi-author major texts suffer from this variation in quality and most such books are very much better in their second edition.

There is a wealth of descriptive material, sometimes excessive, in this book. There are also editorial comments which do not seem to fit comfortably in this type of text. However, such a major textbook will be a useful reference source but it must be noted that there are strong competitors.

British Journal of UROLOGY



BRITISH JOURNAL OF UROLOGY

Journal of the
British Association of Urological Surgeons
and the European Society of Paediatric Urology

Editor

*G. D. CHISHOLM

Honorary Treasurer

*J. P. PRYOR

Editorial Assistant

EDNA MacDONALD

Assistant Editors

R. J. MILLARD

*J. E. NEWSAM

*R. H. WHITAKER

Editorial Committee

Chairman J. H. STEYN*

E. P. ARNOLD, Christchurch
M. HANDLEY ASHKEN, Norwich
M. BHANDARI, Lucknow
*M. C. BISHOP, Nottingham
*J. P. BLANDY, London
A. C. BUCK, Glasgow
C. A. C. CHARLTON, Bath
D. J. DU PLESSIS, Pretoria
*J. M. FITZPATRICK, Dublin
J. C. GINGELL, Bristol
J. A. GOSLING, Hong Kong
*R. R. HALL, Newcastle upon Tyne
T. B. HARGREAVE, Edinburgh
*†K. HJÄLMÅS, Gothenburg
W. F. HENDRY, London
D. KIRK, Glasgow
V. R. MARSHALL, Adelaide

*A. R. MUNDY, London
D. E. NEAL, Newcastle upon Tyne
P. H. O'REILLY, Stockport
K. F. PARSONS, Liverpool
W. B. PEELING, Newport
A. RIZVI, Karachi
*R. J. MORGAN, London
†H. J. F. R. SERUCA, Lisbon
T. SHERWOOD, Cambridge
F. P. SOONAWALLA, Bombay
D. F. M. THOMAS, Leeds
H. N. WHITFIELD, London
J. E. A. WICKHAM, London
GORDON WILLIAMS, London
*R. E. WILLIAMS, Leeds
C. R. J. WOODHOUSE, London
P. H. L. WORTH, London

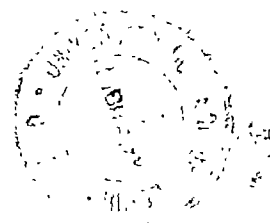
*Member of Executive Committee

†Member of E.S.P.U.

Former Editors

H. P. WINSBURY-WHITE, 1929-1948
D. BAND, 1949-1966
J. D. FERGUSSON, 1967-1972
W. KEITH YEATES, 1973-1977

Churchill Livingstone 



Instructions to Authors

The *British Journal of Urology* welcomes original contributions on urological subjects from all parts of the world. Papers are accepted for consideration on the understanding that their contents have not been published in whole or in part elsewhere, that they are subject to editorial revision, and that the Editor is responsible for the order of publication. Papers on nephrology, of interest to the urological surgeon, are welcome. When relevant, authors must include a statement on the ethical aspects of their research.

Manuscripts. Papers should be submitted in **Journal style**. Failure to do so may lead to significant delays in publication. Papers should be typewritten in double spacing on A4 paper (21 × 29.7 cm) with a margin of at least 3 cm all round. **Two copies of the manuscript and illustrations should be submitted** and the author should retain a copy for reference.

Authorship. All authors must give signed consent to publication. Only those who have made a substantial contribution to the work should be designated as authors and a maximum number of five is preferred. Those who have made a smaller contribution should be recognised separately in the Acknowledgements section.

Original articles should be set out as follows, with each section beginning on a separate page: title page, summary, text, references, authors' page, tables, legends to illustrations.

The **title page** should give the following information: (1) title of article, (2) initials and names of each author, (3) the department and institution to which the work should be attributed.

The **summary** should consist of very brief statements about each of the main sections.

A list of 3 to 6 **key words** should be provided.

The **text** should be arranged as follows: (1) Introduction, (2) Patients and Methods, or Materials and Methods; (3) Results; (4) Discussion and Conclusions, (5) Acknowledgements.

References. The author is responsible for the accuracy of his references. When quoted in the text they should include the author's name and year of publication. In the case of 2 authors both names should be cited. If there are more than 2 authors, only the first author plus *et al.* should be quoted. The list of references at the end of the paper should be in alphabetical order and should give the names of *all* authors unless there are more than three, when only the first three should be given followed by *et al.* With journal references the following sequence should be observed: name(s), initials; date, title of paper, name of journal *abbreviated according to Index Medicus*; volume number, first and last page numbers. Thus:

Morris, J. A., Oates, K. and Staff, W. G. (1986). Scanning electron microscopy of adenomatoid tumours. *Br J Urol.*, 58, 183–187.

References to books should be as follows:

Wright, F. S. and Howards, S. S. (1981). Obstructive injury. In *The Kidney*, ed. Brenner, B. M. and Rector, F. C. Second edition. Volume II. Chapter 38, pp. 2009–2044. Philadelphia: Saunders.

The **authors' page** should give the names of all authors, their qualifications and main appointment. Please indicate the name and address of the author to whom offprint requests should be made.

Tables should be kept to a minimum and laid out as simply as possible. Each should be typed on a separate sheet, numbered in Arabic numerals and should not duplicate information in the text.

Illustrations. Photographs and radiographs should be submitted in the form of half-plate prints (approximately 17 × 11 cm). All figures should be unmounted. The number of the illustration (in Arabic numerals), the author's names, and the "top" of the illustration should be indicated lightly in pencil on the back. The magnification of photomicrographs and details of staining techniques should be given. Lettering on figures must be indicated on a transparent overlay. Illustrations in colour cannot be accepted unless the author is willing to cover the cost.

Points of Technique and Case Reports should not exceed 250 words, 2 illustrations and 3 references. In **Case Reports** the sections should be (1) Case Report; (2) Comment; (3) References.

Proprietary names of drugs, instruments, etc., should be indicated by the use of initial capital letters.

Abbreviations and units. All measurements should be expressed in S.I. units except blood pressure which will continue to be expressed in mmHg. For more detailed recommendations authors may consult the Royal Society of Medicine publication entitled *Units, Symbols and Abbreviations: A guide for Biological and Medical Editors and Authors*.

Correspondence. Questions or comments concerning recently published papers may be sent to the Editor, who will refer them to the authors. The readers' comments and authors' replies may subsequently be published together in the Correspondence column.

Address. All editorial communications, including books for review, should be addressed to the Editor, Professor G. D. Chisholm, Western General Hospital, Edinburgh EH4 2XU.

Offprints. Twenty-five free offprints are supplied to the author to whom offprint requests are to be made. Order forms will be sent with the proofs for correction, all of which should be returned to the publishers within 7 days of receipt.

Subscriptions. The journal is published monthly by Churchill Livingstone. Institutional rate for 1992 is £90.00 (UK), £100.00 (overseas) or \$180.00 (USA), the Trainee rate is £39.00 (UK), £42.50 (overseas) or \$76.50 (USA) per annum, post free, for non members. Second class postage is paid at Rahway NJ. Postmaster: send USA address corrections to British Journal of Urology, c/o Mercury Airfreight International Ltd Inc, 2323 Randolph Avenue, Avenel, New Jersey 07001.

This journal is indexed, abstracted and/or published on line in the following media: Adonis, Colleague (online), Current Awareness in Biological Sciences, Current Contents, Excerpta Medica, Biological Abstracts, UMI (Microfilms), BRS Colleague (full text), Chemical Abstracts, Modern Medicine, Index Medicus, NMLUIS Reference Up Date and UMI (Disk).

Subscription enquiries: Longman Group U.K. Limited, Subscriptions (Journals) Department, P.O. Box 77, Fourth Avenue, Harlow, Essex CM19 5BQ. Telephone: 0279 623760. For missing copy queries our customer relations team can be contacted on 0279 623924.

Note to Users in the USA. Authorisation to photocopy items for internal or personal use is granted by the copyright holder provided that the appropriate fees are paid directly to Copyright Clearance Center, 27 Congress Street, Salem, MA 01970, USA. For more information, please contact CCC. For territories outside North America, permission should be sought direct from the copyright holder. This consent does not extend to other kinds of copying, such as copying for general distribution, for advertising and promotional purposes, for creating new collective works, or for resale.

0007-1331

Copyright © 1992 British Journal of Urology. All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, without the prior permission of the copyright owner, or a licence permitting restricted copying in the United Kingdom issued by the Copyright Licensing Agency Ltd, 90 Tottenham Court Road, London W1P 9HE.

Printed on acid-free Fineblade Smooth 100 gsm paper. The publisher's policy is to use paper manufactured from sustainable forests.

British Journal of Urology

Volume 70 No 2

August 1992

Contents

Review

Lower Urinary Tract Reconstruction in Young Patients

C. R. J. Woodhouse 113

Original Articles

Long-term Follow-up of Patients with Hydronephrosis Treated by Anderson-Hynes Pyeloplasty

S. S. Mikkelsen, B. S. Rasmussen, T. M. Jensen, W. Hanghøj-Petersen and P. O. Christensen 121

Renal Carcinoma in Patients Undergoing Nephrectomy: Analysis of Survival and Prognostic Factors

A. P. Sene, L. Hunt, R. F. T. McMahon and R. N. P. Carroll 125

Blood Transfusion and Survival Following Surgery for Renal Carcinoma

T.-H. Edna, K. Vada, F. Hesselberg and O. K. Mjølnerød 135

Ureteric Complications of Renal Transplantation

S. H. Kashi, J. P. A. Lodge, G. R. Giles and H. C. Irving 139

Voiding Dysfunction and Urodynamic Findings in Patients with Cervical Spondylotic Spinal Stenosis Compared with Severity of the Disease

T. L. J. Tammela, M. J. Heiskari and O. A. Lukkarinen 144

Acute Urinary Retention. Comparison of Suprapubic and Urethral Catheterisation

A. F. Horgan, B. Prasad, D. J. Waldron and D. C. O'Sullivan 149

In vivo Detection by Microscopic Chromocystoscopy of Concurrent Urothelial Atypia in Superficial Bladder Cancer

A. Iguchi, N. Kinoshita and Z. Masaki 152

Urological Audit: the Role for an Aggressive Approach to High Grade Superficial Bladder Tumours

S. R. Mohamed, S. F. Mishriki, R. A. Persad, P. Abrams, J. C. Gingell and R. C. L. Feneley.. . . . 156

Initial Combination Chemotherapy with Cisplatin, Methotrexate and Vinblastine in Locally Advanced Transitional Cell Carcinoma—Response Rate and Pitfalls

S. D. Fossa, S. J. Harland, S. B. Kaye, D. Raghavan, J. M. Russell, M. K. B. Parmar, Barbara M. Uscinska, R. Wood and the MRC Subgroup in Advanced Bladder Cancer (on behalf of the MRC Urological Working Party) 161

Intravesical Instillation of Beta-Interferon in the Treatment of Bladder Cancer

R. Migliari, M. El Demiry, G. Muscas and E. Usai 169

Transurethral Incision versus Transurethral Resection of the Prostate. A Subjective and Objective Analysis

P. F. Soonawalla and D. S. Pardanani 174

Localised Deep Microwave Hyperthermia in the Treatment of Benign Prostatic Hyperplasia: Long-term Assessment

A. Yerushalmi, D. Singer, R. Katsnelson, E. Levy and A. Shani 178

Inter-relation between Measurement of Serum Prostatic Specific Antigen and Transrectal Ultrasound in the Diagnosis of Benign Prostatic Hyperplasia and Prostatic Cancer	
R. Clements, R. J. Etherington, G. J. Griffiths, W. B. Peeling, H. Hughes and M. D. Penney	183
Laparoscopic Ligation of Internal Spermatic Vein	
Ming-Tsun Chen, Allen Wen-Hsiang Chiu and Luke S. Chang	188
Urine Transparency as an Index of Absence of Infection	
Gabrielle Phillips, Laura W. Fleming, I. Khan and W. K. Stewart	191
 Paediatric Urology	
Current Management of Duplex-System Ureterocele: Experience with 41 Patients	
A. M. K. Rickwood, I. Reiner, M. Jones and C. Pournaras	196
 Case Reports	
Posterior Urethral Valves in Non-twin Siblings	
P. A. Borzi, S. W. Beasley and R. Fowler	201
Two Rare Genital Abnormalities: Crossed Testicular and Scroto-testicular Ectopia	
H. Doğruyol, M. Özcan and E. Balkan	201
Regression of Lymphadenopathy in Patient with Prostatic Carcinoma after Hormonal Manipulation	
C. Constantinides, G. Alivizatos, D. Mitropoulos and C. Dimopoulos	203
Right-sided Varicocele Caused by False Aneurysm from Aortic Graft	
M. P. Corlett, B. R. Gwynn and J. D. Hamer	204
Primary Actinomycosis of the Urinary Bladder	
A. P. Makar, J.-P. Michielsen, G. J. Boeckx and E. A. Van Marck	205
Extraskelatal Ewing's Sarcoma Metastatic to Penis	
J. Jiménez-Verdejo, P. L. Fernández, A. Haddad, A. Garcia-Carriazo, A. Zuluaga and F. Nogales	206
Haematuria after Exercise following Pelvic Fracture	
L. Jones and R. C. L. Feneley	207
Laparoscopic Removal of Intra-abdominal Testis	
L. H. Stewart, R. N. Heasley and W. G. G. Loughridge	208
 Points of Technique	
The Rat-tail Catheter in Ureteroneocystostomy Operations	
K. Anafarta, T. Yurdakul and Y. Beduk	210
The Autoinjector Device: An Aid to Intracavernosal Pharmacotherapy	
H. W. Gilbert and J. C. Gingell	211
Suprapubic Catheterisation and Bowel Injury	
A. Parikh, C. R. Chapple and S. J. Hampson	212
Nephrostomy Tubes Resistant to Removal	
L. H. Stewart, R. M. Kernohan and W. G. G. Loughridge	213
Localisation of Intra-abdominal Testis by Magnetic Resonance Imaging	
K. M. T. Ho, M. L. Nicholson, M. L. Wastie and P. W. Wenham	215
Correspondence	216
Notices	217
Diary	218
Book Reviews	220

REVIEW

Lower Urinary Tract Reconstruction in Young Patients

C. R. J. WOODHOUSE

Institute of Urology; Departments of Urology, St George's Hospital and Royal Marsden Hospital, London

There are now very few indications for a permanent cutaneous urinary diversion in a child. Many congenital anomalies of the lower urinary tract can be completely reconstructed. The neuropathic bladder can be made continent and "safe" for the kidneys. For some patients continent diversion avoids the need for a cutaneous appliance.

In the past, however, diversion was sometimes a life-saving procedure and in other patients the only practical method of managing incontinence or recurrent urinary infection. In young adults, the reconstructive techniques that are used now in children can be applied to get rid of the bag. Almost anyone can have a reconstruction, but as the original surgery may have included resection of some of the urinary tract, more extensive and imaginative techniques may be needed.

Before undertaking such surgery it is important to consider the possible long-term benefits. The only certain improvement is cosmetic: the patient will have no external appliance. If the bladder is neurologically normal the long-term results of undiversion should be good. Some patients will be able to void normally but others may need to empty the bladder by intermittent clean self-catheterisation (ICSC).

The long-term results of cutaneous diversion are poor, whilst the late results of complex reconstructions, especially those using bowel, are yet unknown. Some infective and metabolic complications are becoming apparent. It is salutary to remember that ureterosigmoidostomy had been used for nearly 100 years before the risk of neoplasia was really appreciated.

Those who undertake such surgery must be sure that the parents and patients know of the uncertain future and the need for careful follow-up.

Older patients should not be deprived of such surgery just on grounds of age. However, care is needed to select patients who are both physically and emotionally fit enough.

Principles of Lower Urinary Tract Reconstruction

When one or more components of the lower urinary tract are unusable, imagination is needed to devise a system that avoids an external bag. Reconstruction should be tailored for each patient. There are 3 components to be considered and they are largely independent of each other: a reservoir for the urine, an outlet to the surface and a continence mechanism. The anatomical structures that have been used for each of these are shown in the Table. It can be seen that the reservoir may be made from one or more of the structures in the first column and the outlet from one in the second column (lengthened by a skin tube if necessary); the continence mechanism is indicated from column 3. The reconstructed system may be emptied by ICSC or by spontaneous voiding.

Simple reconstruction or undiversion has now become routine and will not be considered further. Even for complex reconstructions, however, the reservoir should include as much normal bladder as

Table Tissues Used in Reconstruction of the Lower Urinary Tract

<i>Reservoir</i>	<i>Conduit</i>	<i>Control system</i>
Bladder	Urethra	Urethral sphincters
Stomach	Appendix	Mitrofanoff
Ileum	Fallopian tube	Kock
Caecum	Ureter	Ileocaecal valve
Colon	Skin tube	Benckroun
	Ileum	Artificial sphincter
	Umbilical vein	

possible. The urethra remains the best outlet. The natural sphincters, if they can retain urine, are the best control mechanism.

Otherwise the choice of reconstruction depends on the material available, the needs of the patient, the possibilities for follow-up and the skill of the surgeon. It is a mistake to confine oneself to a single system, such as a particular type of pouch, because none is suitable for all patients. Furthermore, there are many occasions when a planned reconstruction must be changed mid-operation if a component is found to be unusable.

Choice of Reservoir

Bladder is the natural reservoir for urine and should only be abandoned if irreversibly diseased, a rare circumstance in children and adolescents. The bladder may be removed for cancer or when damaged by radiotherapy or cyclophosphamide. In endemic areas, bilharzia or tuberculosis can destroy the bladder. Chronic interstitial cystitis is occasionally seen in adolescents. In exstrophy and its variants the bladder may be too small (particularly after a failed reconstruction) to be worth saving.

Adolescent females with a congenital neuro-pathic bladder are an exceptional group in whom it is not wise to retain a large bladder remnant. Five of 16 in my own series had problems from the residual native bladder. In one there was persistent hyper-reflexia. In 4 patients hyper-reflexia was unmasked by sexual activity: orgasm in 3 and sexual arousal in 1. Therefore, if bladder emptying is likely to be by ICSC, a good case can be made for using a substitution cystoplasty (Woodhouse, 1992).

If the bladder is small, poorly compliant or at high pressure, some bowel may be added (augmentation cystoplasty) or may completely replace the bladder (substitution cystoplasty).

A small bladder must be considered in relation to the ureteric and urethral junctions. If there is no ureteric reflux or obstruction and the outlet is continent, the small bladder may be an ideal base for reconstruction. It is usually difficult to reimplant the ureters into such a bladder, though it may be possible to reconstruct the outlet for incontinence.

If there is no bladder (or if it is to be abandoned), a new reservoir must be constructed from intestine. If there is an existing conduit, it should be incorporated. There is no consensus on the choice of bowel for a urinary reservoir, except that jejunum is too metabolically active for general use; 40 cm of small intestine, 20 cm of large intestine or a

combination can make a low pressure substitute of adequate volume.

The stomach may be useful in children with renal failure because of the acid that is secreted (Adam *et al.*, 1988). However, if the child then becomes anuric, the continued secretion of acid into an otherwise "dry" bladder may cause irreversible damage.

The intrinsic peristaltic contractions must be abolished. I believe that this is best achieved by longitudinal incision through the full thickness of the bowel wall. The opened-out bowel is then re-configured to form a reservoir which is as near spherical as possible (Hinman, 1988).

Gonzales *et al.* (1986) used bowel without transection of the muscle and gave anticholinergics to suppress peristalsis in the 50% of patients who had unacceptably high pressures. Alternatively, a very long segment of bowel may be used, so that the volume of urine stored is never large enough to stimulate high pressure contractions (Mundy, 1988a).

Urodynamic studies have shown that the lowest pressures are achieved with an ileal patch augmentation of a colonic bladder (Lytton and Green, 1989).

It is not always possible to abolish peristalsis even by complete transection of the circular muscle. I have also encountered 2 patients who re-established high pressure peristalsis after a period of bowel inertia. I have not found anticholinergic drugs to be effective.

In follow-up, the ileum appears to have a greater metabolic activity but a lesser risk of spontaneous rupture than colon. However, the differences are insufficient to dictate a particular choice.

As lower urinary tract reconstruction becomes more complex in its surgery, so the choice of technique becomes more difficult.

The Outlet

The urethra is the natural outlet for urine and the only one that will allow spontaneous voiding. The urethra is more dependent on its continence mechanism than other possible outlets. Together, the urethra and its sphincters form the ideal system, but it can be difficult to predict whether they will be competent or usable after bladder reconstruction. Grossly abnormal bladders are often associated with other major abnormalities.

Firstly, the substituted bladder cannot always be emptied to completion, so that ICSC may be

necessary. Patients with a neuropathic bladder which is so poor that substitution is necessary are often severely affected with myelomeningocele. They may lack the manual dexterity to self-catheterise. The problem is worse if they walk with 2 crutches or are wheel-chair bound. If the bladder is not neuropathic but has been damaged, for example, by cyclophosphamide or surgery, the urethra, especially in the male, may be too sensitive for ICSC.

Secondly, the urethral sphincters may be incompetent, so that either an artificial sphincter (AUS) or a bladder neck reconstruction will be necessary. The feasibility and desirability of these procedures must be taken into account before deciding to anastomose the pouch to the urethra.

Thirdly, if an adolescent boy has had a lifelong diversion, his penis will only ever have been a sexual organ. If, after undiversion, he needs to self-catheterise, the philosophical question arises as to whether he should catheterise his sexual organ. It seems unlikely that there is a "right" answer to this question.

The site of a catheterisable stoma should be chosen chiefly for the patient's convenience: the urethra should only be used as the outlet if it is clearly superior to a suprapubic continent stoma.

If there is no usable urethra the choice lies between constructing one or using a technique of continent diversion with a suprapubic catheterisable stoma. It is possible completely to reconstruct the urethra from labia, penile skin or pedicled ureter. The tube is then tunnelled into the reservoir to make a continent outflow. The bladder is usually emptied by ICSC but spontaneous voiding is sometimes (Mitchell *et al.*, 1988; Mundy, 1988b). Such intricate reconstruction is only occasionally indicated.

A new outlet can be constructed from almost any tube. If a wide bore tube (such as ileum) is used, its continence system must involve some kind of intussusception, unless it is tailored. Narrow tubes must be tunnelled into the reservoir to produce continence.

Of the narrow tubes the appendix is the easiest to use and appears to be the most resilient. A slightly dilated ureter is also satisfactory, but a completely normal one may be difficult to dilate to a diameter suitable for catheterisation. The lateral two-thirds of the fallopian tube are also satisfactory but are seldom available. A tube can also be made from pedicled skin to use alone or with anastomosis.

The ileum is the standard wide tube and is generally the easiest to catheterise.

Continence Systems

If the urethra is the ideal outlet, the urethral sphincters should be the best continence system.

In diverted patients, they must be tested and preparation should include an examination under anaesthesia and insertion of 2 suprapubic catheters. Several days can then be spent filling the bladder with water and testing the sphincter function—so-called "bladder cycling". Urodynamics are performed when a stable state is reached. Neurologically normal sphincters should allow complete emptying after enterocystoplasty. Even in patients with the neuropathic bladder of spina bifida, I have found that function was correctly predicted in 79% of patients by this simple investigation (Woodhouse, 1992). Using the more sophisticated techniques of fluoroscopy of the internal sphincter and electromyography of the external sphincter, correct function was predicted in 93% of patients (Gonzalez and Sidi, 1985).

In assessing the bladder/sphincter function as a whole, especially in patients with neuropathies, Wang *et al.* (1988) emphasised the importance of the "leak point pressure". That is the intravesical pressure at which leakage occurs through the urethral sphincters. If the leak point pressure is above 40 cm of water, upper tract deterioration is likely, probably because of progressive loss of bladder compliance. Conversely, as a bladder reconstructed by enterocystoplasty usually has a resting pressure below 30 cm of water, such powerful sphincters should maintain continence.

In my experience, young adults with normal sphincters have been continent after bladder substitution. However, in older patients some authors have found day or night incontinence. The main cause has been persistence of mass peristalsis even in detubularised bowel. Most of the reported patients were elderly and all had had a cystectomy; both of these factors may have had an adverse effect on sphincter function (Lytton and Green, 1989).

If the sphincters are continent but do not allow complete emptying, ICSC is generally the best management. There is sometimes pressure on the surgeon to arrange for "normal" voiding. To achieve this it would be necessary to destroy the natural sphincters and to implant an AUS. In most cases this seems unwise. Even with an AUS, complete voiding cannot be guaranteed after enterocystoplasty and ICSC may still be necessary. The long-term results of AUS are unknown. Should the AUS become infected and require removal, the

patient would be continually incontinent and worse off than he was originally: the options for further reconstruction would then be limited. Finally, in units performing large numbers of these operations, many of the patients come from remote parts of the world where "servicing" of a faulty AUS might be impossible.

If the sphincters are incontinent, the options are to reconstruct the bladder outlet to create continence or to use an AUS. A good case can be made for either of these. However, units have tended to use either one or the other and so it is difficult to establish indications for each. For example, Gonzalez and Sidi (1985) reported the use of the Young-Dees bladder neck reconstruction in 8 patients with incompetent sphincters, 7 of whom were continent on ICSC. The AUS had been used in other patients with success, but the need for "servicing" and doubts about the mechanism's longevity favoured the Young-Dees. Mitchell and Piser (1987) reserve the AUS for patients who can demonstrate complete bladder emptying.

Both Mundy *et al.* (1986) and Galloway *et al.* (1987) have reported good results with undiversion using an AUS (Brantley Scott 792 or 800). There were 36 patients in their 2 series. Virtually all were able to void to completion. Up to 7 were at least partly incontinent. There were 8 sphincter complications that required reoperation. At least in patients with neuropathic bladder, the trend has been away from sphincterotomy and the AUS in favour of ICSC (Parry *et al.*, 1990).

The long-term results of ICSC are good. When Diokno *et al.* (1983) reviewed patients after 10-years' follow-up, only 2 of 60 patients had given up catheterising because of a complication. Thirty others had been lost to follow-up, died or suffered a change in neurological status. However, the urethra can be damaged so badly that the technique has to be abandoned. The risk is greater if the urethra has no sensation. Development of a false passage is a particular problem and can be difficult to treat: 2 of 9 patients in one series had to have a continent diversion because of this complication (Koleilat *et al.*, 1989).

Attempts to make a continent bladder neck and urethra which also allow complete spontaneous voiding have met with mixed results. It is difficult to balance the outflow resistance against the intravesical pressure. Furthermore, there must be enough good bladder tissue to allow the reconstruction to be done (not a common circumstance in children presenting for reconstruction).

In a 10- to 22-year follow-up of patients who had

bladder neck reconstruction (but who had not been diverted), 19 of 27 children were completely dry and 1 had stress incontinence. One child emptied by ICSC, but the rest voided normally (Leadbetter, 1985). This is probably the best result and longest follow-up available for such reconstructions. Those who claim success for more complex methods must compare their results with it.

Without the urethral sphincters, there are 2 basic principles that may be applied to create continence: either a flutter valve made by the intussusception of a wide bore tube (Kock, 1971) or a flap valve made by the tunnelling of a narrow tube into the wall of the reservoir (Mitrofanoff, 1980).

There are several variations on these themes, in some cases amounting to completely new designs (Gleeson and Griffith, 1990). The Indiana system is based on the competence of the ileocaecal valve (Rowland *et al.*, 1987). However, the terminal ileum which forms the conduit is tailored and may even be buried in the pouch wall, which makes the whole design very similar to that of the Mitrofanoff procedure.

In the Benckroun system a length of ileum is intussuscepted but with the serosal surface being turned inwards to form the catheterisable tract, unlike the Kock procedure where the mucosal surface forms the tract (Benckroun *et al.*, 1989).

Our own studies have shown that the resting pressure generated within a Mitrofanoff conduit is 2 to 3 times the highest pressure generated by the reservoir. Furthermore, the conduit responds to pouch pressure rises with a considerable pressure rise of its own. The difference between the conduit pressure and the pouch pressure is large, so that continence is reliably maintained. In Kock nipples the difference between conduit and pouch pressures is small and the response to pouch pressure rises is limited, so that continence is tenuous. These experimental observations in patients have mirrored my clinical experience: it is much easier to make a continent Mitrofanoff than a continent Kock (Cumming *et al.*, 1987).

Nonetheless, all of the various systems are used with enthusiasm by their proponents. They can all be made to work but there must be lessons in construction that can only be learnt with personal practice. It can be difficult to assess the continence rates from the published data because some authors give a complication rate without specifying details and others give a continence rate after revision operations. The latest published continence rates for the various systems range from 86 to 100%.

As a last resort, the AUS may be considered to

give continence to a reconstructed outlet. The cuff of an artificial sphincter is designed to encircle a normal urethra or bladder neck. Experimental evidence suggests that AUS cuffs can be placed safely around intestine providing the pressure is low (Engelmann *et al.*, 1985). An AUS with a cuff pressure of 71 to 80 cm has been used successfully around large bowel in 3 of 4 children with a maximum follow-up of 11 years (Light, 1989).

In the reconstructed urethra the greatest experience is in patients with exstrophy. In the series reported by Decter *et al.* (1988), 10 of 16 patients retained their device, 9 of whom were continent. Ten revision procedures were necessary to achieve even this result. Although these results are poor, the patients were a difficult group, having failed numerous other attempts to achieve continence.

As with undiversion, imagination must be used to produce the best system for each patient. It is a mistake to become addicted to a single complete system and to use it exclusively: the problems encountered in children and adolescents are varied and the correct combination of reservoir, outlet and valve must be chosen for each.

General Consequences of Reconstruction

Storage and emptying

In the short term, it has been shown that the reconstructed bladders of children and adolescents can store urine and can be emptied spontaneously or by ICSC. Those that have been diverted can be undiverted. If all else fails a continent internal diversion is an acceptable alternative.

The surgery required is technically taxing. The complication rate is 25 to 30%. Most of the complications requiring reoperation have been related to the continence mechanism rather than to the cystoplasty (Gonzales *et al.*, 1986).

As always with the young, it is essential to consider the long-term results. For the complex reconstructions and undiversions, there seem to be only about 76 children in the literature who have been followed up for at least 5 years. It is difficult to pick out their details from the mass of data about a variety of different patient types (Woodhouse, 1991). The good results for continence are maintained but complications related to storage are becoming apparent.

Rupture of reservoir

The incidence of spontaneous rupture varies between different units. When it does occur, the

consequences are devastating. There may be delay in diagnosis, although the history of sudden abdominal pain and diminished or absent urine drainage should make it obvious. The patient rapidly becomes very ill with generalised peritonitis.

"Cystogram" is commonly normal. Diagnosis is best made by ultrasonography and peritoneocentesis of fluid collections.

If diagnosed early, catheterisation and broad spectrum antibiotics may lead to recovery. If the patient fails to respond rapidly to this regime or if there has been delay in diagnosis, laparotomy should be performed at once. In one series 1 of 4 patients died (Rushton *et al.*, 1988).

Patients and their families should be warned of this possible complication and advised to return to hospital at once if there are any symptoms of acute abdomen, especially if the reservoir stops draining its usual volume of urine.

Pregnancy

When reconstructing females it is essential to consider the possibility of a future pregnancy. The "bladder" should be made to lie anteriorly in the abdomen. The bowel pedicle should be fixed on one side to allow enlargement of the uterus on the other.

Pregnancies after any type of undiversion or lower tract reconstruction with bowel are rare so far. They may be complicated and require the joint care of obstetrician and urologist (Hill and Kramer, 1989). Particular problems include upper tract obstruction and changes in bladder control as the uterus enlarges, and damage to the bladder outlet during vaginal delivery. It is tempting to recommend caesarean section but only with a urologist present who can protect the bowel pedicle from damage.

Pregnancies after continent diversion have not yet been reported in the literature. There has been a successful one in my own series and another from Philadelphia, both following Mitrofanoff procedures (Duckett, personal communication).

Metabolic changes

Metabolic changes are common when urine is stored in intestinal reservoirs and must be carefully monitored. Nurse and Mundy (1989a) made an experimental study of the handling of electrolytes instilled into intestinal reservoirs and subsequent arterial blood gas analysis. All patients were found to absorb sodium and potassium from the reservoirs but the extent was variable. A third of all patients

(but 50% of those with an ileocaecal reservoir) had hyperchloraemia. All patients had abnormal blood gases, the majority having metabolic acidosis with respiratory compensation. The findings were unrelated to either renal function or to the time that had elapsed since the reservoir was constructed.

In 106 children and adolescents at St Peter's Hospitals who had any form of enterocystoplasty, hyperchloraemic acidosis (HCA) was found in 14 (13%) and borderline HCA in 25 (24%). The incidence was lower in reservoirs with ileum as the only bowel segment when compared with those containing some colon (9 vs 20%). When arterial blood gases were measured in 29 of these children no consistent pattern was found (Wagstaff *et al.*, 1991).

A further area that might give concern is the consequence of removing the ileocaecal valve and terminal ileum from the intestinal tract to use in the bladder reconstruction. Although the remainder of the ileum is known to have considerable ability to adapt, there have been fears that patients would develop macrocytic anaemia or chronic diarrhoea. In practice these fears seem to have been unfounded.

There have been no clinical problems in my own patients: 8% were found to be anaemic but none had macrocytaemia or folate deficiency. In an experimental study in patients with reservoirs between 8 months and 8 years old, no disturbance of B₁₂ or carotene metabolism was found (Canning *et al.*, 1989). In Kock pouch patients followed up for 5 to 11 years, 6 of 17 patients were found to have borderline or subnormal B₁₂ levels requiring supplements (Akerlund *et al.*, 1989).

It is particularly important to note that the reservoirs retain their ability to alter body metabolism for years. Where Nurse and Mundy (1989a) detected changes they were unaffected by the age of the reservoir.

Renal function

In the follow-up so far available, undiversion or continent diversion seem not to have affected renal function. When function has improved after such surgery it is likely to be the result of eliminating obstruction or high bladder storage pressure.

In the longer term, renal deterioration has been related to obstruction, reflux and stone formation. In one long-term study of Kock pouch patients, these complications occurred at the same rate as that found in patients with ileal conduits: 29% at 5 to 11 years (Akerlund *et al.*, 1989).

Infection and stones

Stones are a particular problem in reservoirs containing metal staples (such as the Kock). Otherwise, stones in the reservoir are associated with infection and retained mucus. In our patients, 28% have troublesome urinary infections and a further 20% have occasional infections. Renal stones have developed in 1.6% of patients of all ages and reservoir stones in 12% (Wagstaff *et al.*, 1991).

The significance of infection alone is uncertain. In the long-term follow-up of patients practising ICSC on non-reconstructed bladders, 11% were found to have chronic bacteriuria (Diokno *et al.*, 1983). It has been said that such infection is harmless except in the presence of high grade reflux, when 60% of patients suffer renal damage (Kass *et al.*, 1981). In ileal conduits, however, persistent infection, especially with *Escherichia coli*, has been associated with progressive renal scarring (Bergman *et al.*, 1979).

Growth

The most worrying consequence of enterocystoplasty in children has been delayed growth in height. The data are far from complete. In a series of 60 children, Wagstaff *et al.* (1992) found delay in linear growth in 20%, while growth in weight was normal. There were no metabolic or infective complications to account for this finding. Mundy (personal communication) reported 3 other children who had delayed growth after ileocystoplasty.

Cancer

It is the constant fear of surgeons who carry out these operations on the young that history will repeat itself: the bowel segments will develop neoplasia in the same way that the ureterosigmoidostomy does. Evidence from animal studies suggests that faecal and urinary streams must be mixed for neoplasia to occur. However, if it is chronic mixed bacterial infection, rather than the faeces *per se*, that is required, the bowel urinary reservoir may be at risk.

In 23 patients with colonic and ileal cystoplasties, high levels of nitrosamines were found in the urine (Nurse and Mundy, 1989b). Biopsies of the ileal and colonic segments showed changes similar to those found in ileal and colonic conduits and in ureterosigmoidostomies. More severe histological changes and higher levels of nitrosamines correlated with heavy mixed bacterial growth on urine culture.

Single cases of pouch neoplasms have been reported. In a review of the literature, 14 cases were identified by Filmer and Spencer (1990). Special features could be found in nearly all cases. For example, 10 patients had been reconstructed for tuberculosis; 4 tumours were not adenocarcinomas; 1 patient had a pre-existing carcinoma; 6 patients were over 50 years old. Nonetheless, cancer does occur in enterocystoplasties at a mean of 18 years from construction. This is a few years earlier than the mean time at which malignant neoplasms are seen in ureterosigmoidostomies.

Cancer must remain a cause for great vigilance in the follow-up of patients. It is interesting to note that no cases have been reported from units routinely performing large numbers of these operations.

Psychological consequences

There has been no study of the psychological consequences of lower urinary tract reconstruction in children. Apart from the trauma of major surgery, it seems probable that successful reconstruction in a young child could only be beneficial. Similarly good results could be expected when getting rid of a cutaneous diversion in a child.

In adolescents, particularly those who have been diverted all of their lives, the generally good outcome has been tempered with the occasional and unexpected disaster. Most surgeons with wide experience of undiversion have a patient who, while not wishing to have the bag back, is disturbed by the new arrangement.

Conversely, a problem arises with the "disaffected teenager". His many social and psychological problems are blamed by his family and doctors on "growing up" and by the patient on his stoma. The greatest care must be taken in the assessment of these patients, but occasionally I have found that the patient's view was correct: all was solved by getting rid of the stoma.

In a formal psychological assessment of their patients, Boyd *et al.* (1987) found some surprising facts. They compared those who had had ileal conduits with those who had had a Kock pouch. A small subgroup had been converted from conduit to Kock. The majority of patients had cancer and were past middle age. There was little difference in the levels of satisfaction and of physical activity between the 2 main groups. Significantly for the adolescent, however, was the finding that the Kock patients had a better self image, had more physical contact with others and more sexual activity. The subgroup who had had a conversion from conduit

to Kock were almost uniformly extremely satisfied by the result.

References

- Adams, M. C., Mitchell, M. E. and Rink, R. C. (1988). Gastrocystoplasty: an alternative solution to the problem of urological reconstruction in the severely compromised patient. *J. Urol.*, **140**, 1152-1156.
- Akerlund, S., Delin, K., Kock, N. G. *et al.* (1989). Renal function and upper urinary tract configuration following urinary diversion to a continent ileal reservoir (Kock pouch). *J. Urol.*, **142**, 964-968.
- Benckroun, A., Essekal, N., Falk, M. *et al.* (1989). Continent urostomy with hydraulic ileal valve in 136 patients: 13 years of experience. *J. Urol.*, **142**, 46-51.
- Bergman, B., Kaliser, B. and Nilsson, A. E. (1979). Urinary diversion and urinary tract infection. *Scand. J. Urol. Nephrol.*, **13**, 65-70.
- Boyd, S. D., Feinberg, S. M., Skinner, D. G. *et al.* (1987). Quality of life survey of urinary diversion patients. *J. Urol.*, **138**, 1386-1389.
- Canning, D. A., Perman, J. A., Jeffs, R. D. *et al.* (1989). Nutritional consequences of bowel segments in the lower urinary tract. *J. Urol.*, **142**, 509-511.
- Cumming, J., Worth, P. H. L. and Woodhouse, C. R. J. (1987). The choice of suprapubic continent catheterisable stoma. *Br. J. Urol.*, **60**, 227-230.
- Decter, R. M., Roth, D. R., Fishman, I. J. *et al.* (1988). Use of the AS800 device in exstrophy and epispadias. *J. Urol.*, **140**, 1202-1203.
- Diokno, A. C., Sonda, L. P., Hollander, J. P. *et al.* (1983). Fate of patients started on clean intermittent self catheterisation therapy 10 years ago. *J. Urol.*, **129**, 1120-1122.
- Engelmann, U. H., Felderman, T. P. and Scott, F. B. (1985). The use of the AMS-AS800 artificial sphincter for continent urinary diversion. 1. Investigations including pressure flow studies using rabbit intestinal loops. *J. Urol.*, **134**, 183-190.
- Filmer, R. B. and Spencer, J. R. (1990). Malignancies in bladder augmentations and intestinal conduits. *J. Urol.*, **143**, 671-678.
- Galloway, N. T. M., Heathcote, P. S., Gately, C. *et al.* (1987). The longer-term results of undiversion. *Br. J. Urol.*, **60**, 51-53.
- Gleeson, M. J. and Griffith, D. P. (1990). Urinary diversion. *Br. J. Urol.*, **66**, 113-122.
- Gonzalez, R. and Sidi, A. A. (1985). Preoperative prediction of continence after enterocystoplasty or undiversion in children with neurogenic bladder. *J. Urol.*, **134**, 705-707.
- Gonzalez, R., Sidi, A. A. and Zhang, G. (1986). Urinary undiversion: indications, technique and results in 50 cases. *J. Urol.*, **136**, 13-16.
- Hill, D. E. and Kramer, S. A. (1989). Pregnancy after augmentation cystoplasty. *J. Urol.*, **144**, 457-459.
- Hinman, F. (1988). Selection of intestinal segments for bladder substitution: physical and physiological characteristics. *J. Urol.*, **139**, 519-523.
- Kass, E. J., Koff, S. A., Diokno, A. C. *et al.* (1981). The significance of bacilluria in children on long term intermittent catheterisation. *J. Urol.*, **126**, 223-235.
- Kock, N. G. (1971). Ileostomy without external appliances: a survey of 25 patients provided with intra-abdominal reservoir. *Ann. Surg.*, **173**, 545-550.
- Koleilat, N., Sidi, A. A. and Gonzalez, R. (1989). Urethral false passage as a complication of intermittent catheterisation. *J. Urol.*, **142**, 1216-1217.

- Leadbetter, G. W.** (1985). Surgical reconstruction for complete urinary incontinence: a 10 to 22 year follow-up. *J. Urol.*, **133**, 205–206.
- Light, J. K.** (1989). Long-term clinical results using the artificial sphincter around bowel. *Br. J. Urol.*, **64**, 56–60.
- Lyttom, B. and Green, D. F.** (1989). Urodynamic studies in patients undergoing bladder replacement surgery. *J. Urol.*, **141**, 1394–1397.
- Mitchell, M. E., Adams, M. C. and Rink, R. C.** (1988). Urethral replacement with ureter. *J. Urol.*, **139**, 1282–1285.
- Mitchell, M. E. and Piser, J. A.** (1987). Intestinocystoplasty and total bladder replacement in children and young adults: follow-up of 129 patients. *J. Urol.*, **138**, 579–584.
- Mitrofanoff, P.** (1980). Cystostomie continente trans-appendiculaire dans le traitement des vessies neurologiques. *Chir. Pediatr.*, **21**, 297–305.
- Mundy, A. R.** (1988a). Cystoplasty. In *Current Operative Surgery—Urology*, ed: Mundy A. R. Chapter 11, pp. 140–159. London: Bailliere Tindall.
- Mundy, A. R.** (1988b). A technique for total substitution of the lower urinary tract without the use of a prosthesis. *Br. J. Urol.*, **62**, 334–338.
- Mundy, A. R., Nurse, D. E., Dick, J. A. et al.** (1986). Complex urinary undiversion. *Br. J. Urol.*, **58**, 640–643.
- Nurse, D. E. and Mundy, A. R.** (1989a). Metabolic complications of cystoplasty. *Br. J. Urol.*, **63**, 165–170.
- Nurse, D. E. and Mundy, A. R.** (1989b). Assessment of the malignant potential of cystoplasty. *Br. J. Urol.*, **64**, 489–492.
- Parry, J. R. W., Nurse, D. E., Boucaut, H. A. P. et al.** (1990). Surgical management of the congenital neuropathic bladder. *Br. J. Urol.*, **65**, 164–167.
- Rowland, R. G., Mitchell, M. E., Bihrie, R. et al.** (1987). Indiana continent urinary reservoir. *J. Urol.*, **137**, 1136–1139.
- Rushton, H. G., Woodward, J. R., Parrott, T. S. et al.** (1988). Delayed bladder rupture after augmentation enteroplasty. *J. Urol.*, **140**, 344–346.
- Wagstaff, K. E., Woodhouse, C. R. J., Duffy, P. G. et al.** (1992). Delayed linear growth in children with enterocystoplasties. *Br. J. Urol.*, **69**, 314–317.
- Wagstaff, E. E., Woodhouse, C. R. J., Rose, G. A. et al.** (1991). Blood and urine analysis in patients with intestinal bladders. *Br. J. Urol.*, **68**, 311–316.
- Wang, S. C., McGuire, E. J. and Bloom, D. A.** (1988). A bladder pressure management system for myelodysplasia—clinical outcome. *J. Urol.*, **140**, 1499–1502.
- Woodhouse, C. R. J.** (1991). Undiversion and alternatives to a cutaneous urinary diversion. In *Long Term Paediatric Urology*. Pp. 97–115. Oxford: Blackwell.
- Woodhouse, C. R. J.** (1992). Reconstruction of the lower urinary tract for neurogenic bladder: lessons from the adolescent age group. *Br. J. Urol.*, **69**, 589–593.

The Author

C. R. J. Woodhouse, MB, FRCS, Senior Lecturer, Institute of Urology; Consultant Urologist, St George's Hospital and the Royal Marsden Hospital, Honorary Consultant Urologist, St Peter's Hospitals and the Hospital for Sick Children, London.

Requests for reprints to: C. R. J. Woodhouse, Institute of Urology and Nephrology, University College and Middlesex School of Medicine, Riding House Street, London W1P 7PN.

Long-term Follow-up of Patients with Hydronephrosis Treated by Anderson-Hynes Pyeloplasty

S. S. MIKKELSEN, B. S. RASMUSSEN, T. M. JENSEN, W. HANGHØJ-PETERSEN and P. O. CHRISTENSEN

Departments of Surgery, Clinical Physiology and Nuclear Medicine, and Radiology, Central Hospital, Holstebro, Denmark

Summary—A series of 21 patients with hydronephrosis (mean age 37 years) underwent an Anderson-Hynes pyeloplasty; a nephrostomy catheter was not used routinely. One patient developed urinary leakage post-operatively but this ceased following insertion of a ureteric catheter. Assessment was carried out after a mean observation time of 85 months. Clinical examination, laboratory investigations, urography and renography were performed pre-operatively and at follow-up. There was no evidence of stones or stenosis in the pelvis. Patients operated upon before the age of 30 years showed improved renal function. All patients had symptoms pre-operatively but only one had symptoms post-operatively. It was concluded that the results of surgical intervention in hydronephrosis are excellent, especially in patients aged less than 30 years.

Hydronephrosis is a descriptive term for dilatation of the renal pelvis due to distal obstruction, including obstruction at the pelviureteric junction (PUJ). Factors said to play a part in the pathophysiology of PUJ obstruction include aberrant blood vessels, valve formation, high origin of the ureter, adhesions and post-inflammatory stricture. Murnaghan (1957, 1958a and b) laid the foundations for a more dynamic aspect as he demonstrated a muscular anomaly in the pelviureteric junction. Djurhus *et al.* (1976) reported alterations in peristalsis at the PUJ and Gosling and Dixon (1978) described an abrupt increase in diameter in that region. Histological examination showed an increase in connective tissue at the junction between the non-dilated and dilated segments. Uncertainty about the aetiology of the condition has resulted in a variety of operative procedures, all of which have been directed towards reconstruction of the pelviureteric junction. Only long-term follow-up studies can assess the effect of operative intervention. The aim of the present study was to carry out a long-term follow-up (minimum 36 months) of patients

with hydronephrosis treated by an Anderson-Hynes pyeloplasty.

Patients and Methods

The study group included 27 patients who fulfilled the requirement of a minimum observation time of 36 months. Three of these patients died from conditions unrelated to the kidney and 3 could not be traced. The remaining 21 patients, 7 men and 14 women, had a mean age of 37 years (range 11–72) at the time of operation. Pre-operatively no patients were symptom-free; 20 had low back pain, 9 had a urinary infection and 2 had haematuria. All were operated on by the same surgeon and underwent an Anderson-Hynes (1949) pyeloplasty with resection of the twelfth ribs and without routine drainage of the ureter or use of a nephrostomy catheter. Two vacuum drains were placed in the flank.

In 2 cases both a splinting ureteric catheter and a nephrostomy catheter were used pre-operatively; in 1 case this was due to the sequelae of infections in the pelvis and in the other patient, an 11-year-old girl, to narrowing of the ureter.

The mean observation time was 85 months (range

44–142). Pre-operatively the patients were evaluated by clinical examination, laboratory investigations, intravenous urography and radioisotope renography. With the following exceptions, these investigations were repeated at follow-up. One patient had direct pyelography pre-operatively instead of intravenous urography; another had an allergic reaction to the contrast agent, so that no follow-up urography was performed, and 1 patient had no pre-operative renography. In 2 patients the pre-operative urograms were either out of date or no longer available. The urograms were classified into 5 grades of hydronephrosis, as described by Bratt *et al.* (1977): normal, moderate, medium, severe and total obstruction.

The renograms were performed either conventionally, using 2 single detectors placed manually facing each renal region from behind with the patient in the supine position, or as gamma camera renography with ^{131}I -Hippuran or $^{99\text{m}}\text{Tc}$ -DTPA. Preoperatively, 17 patients underwent renography using ^{131}I -Hippuran and in 3 patients $^{99\text{m}}\text{Tc}$ -DTPA was used. All post-operative renography was performed with $^{99\text{m}}\text{Tc}$ -DTPA. Pre-operatively the glomerular filtration rate (GFR) was calculated in only 6 patients, using ^{51}Cr -EDTA in 3 cases and $^{99\text{m}}\text{Tc}$ -DTPA in the other 3.

$^{99\text{m}}\text{Tc}$ -DTPA was used to calculate GFR in all patients post-operatively. All renography was carried out in the supine position.

The parenchymal function of each kidney was estimated from the uptake ratio, given by readings of the isotope renography curve during the first 2 minutes of the second phase of the renogram. Based on data previously published by Aurell *et al.* (1971), the following criteria were applied: normal function-ratio >1.4 ; moderately decreased function-ratio 1.2–1.4; severely decreased function-ratio 1.0–1.2; no function-ratio <1.0 .

Results

Pre-operatively, 9 patients had a urinary infection with more than 10^5 *Escherichia coli*, and antibiotic therapy was administered before and after surgery. During operation, aberrant blood vessels to the hydronephrotic kidney were found in 11 patients (in 1 case the accessory vessel was removed); post-inflammatory changes were found in 2 patients and stones in the pelvis of 4. Apart from hydronephrosis, 5 patients had no abnormal findings. The immediate post-operative course was uncomplicated in 16 patients. Of the remaining 5, 1 developed a pyonephrosis which was treated with a ureteric

catheter; 1 had a urinary leak which was treated with a ureteric catheter until the eleventh post-operative day; 1 had a pneumothorax, 1 a superficial wound infection and 1 developed pneumonia. The vacuum drains were removed on the fifth day. The mean post-operative stay in hospital was 11 days (range 7–22). At follow-up all patients had normal haemoglobin and blood pressure. Pre-operative serum creatinine had a mean level of $91\text{ }\mu\text{mol/l}$ (range 67–134); at follow-up the mean level was $83\text{ }\mu\text{mol/l}$ (range 70–113). In only 6 patients was the GFR determined pre-operatively and the mean value was 1.27 ml/s and 1.73 m^2 (range 0.82–1.54); the mean value at follow-up was 1.52 ml/s and 1.73 m^2 (range 0.68–2.28).

One patient continued to have short-term low back pain and 4 had an aversion to excessive fluid intake. One patient had 5–10 erythrocytes and 30–50 leucocytes per visual field and a positive urine culture exceeding 10^6 *Escherichia coli*, but he had no symptoms. He was one of the 9 patients with more than 10^5 *E. coli* pre-operatively. Urine microscopy and urine cultures were negative for all other patients. One patient developed hydro-nephrosis on the contralateral side.

The results of intravenous urography are shown in Figure 1. Only 17 patients had both pre- and post-operative urography. The flow of contrast from the renal pelvis improved in 16 patients and remained unchanged in 1. No evidence of stones or stenosis in the PUJ was found at follow-up urography.

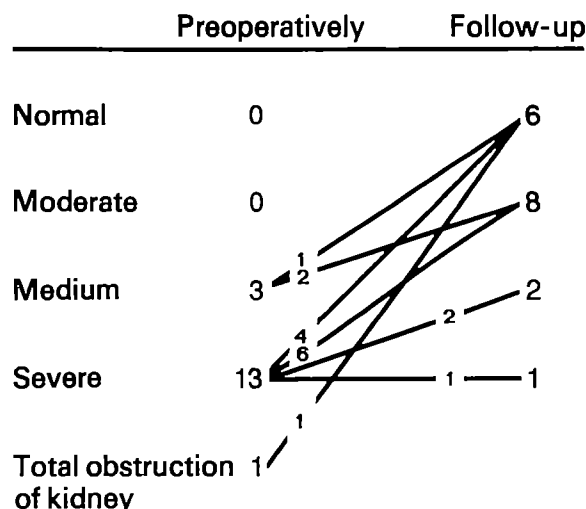


Fig. 1 Classification of hydronephrosis according to the intravenous urogram, before and after reconstruction.

Parenchymal function		Preoperatively	Follow-up
Normal	(>1,4)	2	2
			4
			2
Moderately decreased	(1,2-1,4)	7	5
			9
			4
Severely decreased	(1,0-1,2)	10	6
			7
			1
No function	(<1,0)	1	

Fig. 2 Renographic classification of pre- and post-operative renal parenchymal function on the operated side in 20 patients.

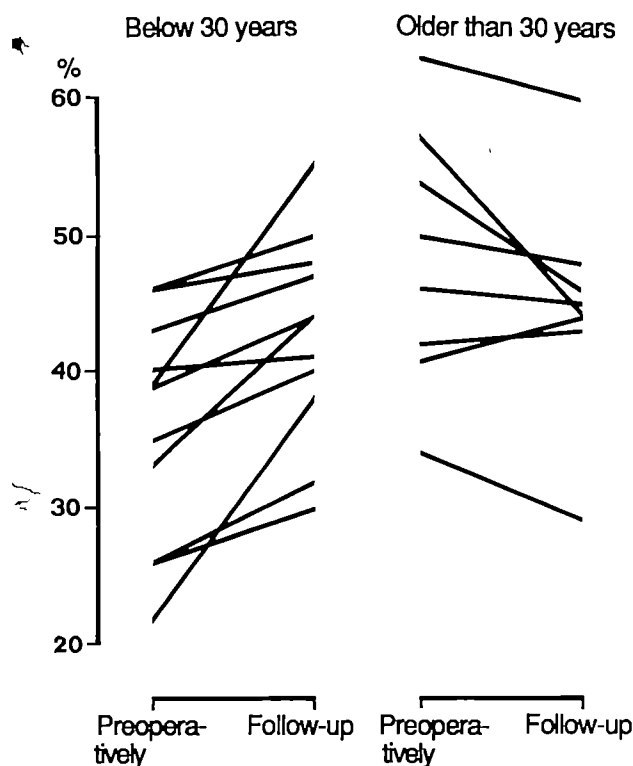


Fig. 3 Pre- and post-operative distribution of renal function on the operated side in 19 patients.

The results of renography are shown in Figure 2. In 20 patients this was carried out both pre- and post-operatively, but in 1 case only post-operatively. Parenchymal function on the operated kidney was found to be either improved or unchanged. Figure 3 shows renal function on the operated side in

patients below 30 years of age compared with that in older patients.

Younger patients showed increased function in the operated kidney but in the others there was a moderate decrease.

Discussion

The purpose of surgical intervention for hydronephrosis is to relieve symptoms and, if possible, to improve renal function. Previously, a nephrectomy was often performed on patients with unilateral hydronephrosis (Culp, 1961), but Roberts *et al.* (1972) and Poulsen *et al.* (1987) showed that renal function could be improved by a pyeloplasty procedure. This seems especially true in the case of younger patients (Roberts *et al.*, 1972; Bratt *et al.*, 1983; Poulsen *et al.*, 1987). The present study showed improved renal function in patients under the age of 30 years. For older patients, the renal function share was moderately decreased at the time of follow-up (Fig. 3).

Pre-operatively all patients had symptoms; post-operatively only 1 patient complained of recurrent low back pain and 4 had a slight aversion to excessive fluid intake. In the present study, with a mean observation period of 85 months, no strictures, stones or "extinct kidney" have been found; this is in accordance with the results of previous studies (Roberts *et al.*, 1972; Bratt *et al.*, 1983).

Urinary leakage appears to be the most frequent complication of pyeloplasty. Bratt *et al.* (1983) found that nephrostomy tended to reduce the incidence, showing that it occurred in 29/64 patients (45%) who underwent pyeloplasty without nephrostomy but in only 4/14 (29%) where nephrostomy was performed per-operatively. Since nephrostomy, as such, was not associated with urinary infection, they recommended its use in the management of idiopathic hydronephrosis. Sunderland (1963) found a higher rate of urinary leakage (68%) without the use of nephrostomy.

In the present study a nephrostomy catheter was not used routinely and was required in only 2 patients, both of whom showed narrowing of the pelviureteric junction. Only 1 patient developed a urinary leak and this was treated with a ureteric catheter for 11 days. We do not recommend the routine use of nephrostomy.

It was concluded that when dealing with patients with PUJ obstruction, chronic urinary infections should be treated with relevant antibiotics. Surgical treatment of hydronephrosis should be undertaken in patients with symptoms and/or impaired renal

function. As shown in the present study and in those by Poulsen *et al.* (1987) and Tveter *et al.* (1975), renography carried out 12 months post-operatively revealed normal drainage and stable or improved function; these results can be regarded as final proof of the success of the procedure. This study confirms longterm success of the procedure

References

- Anderson, J. C. and Hynes, W. (1949). Retrocaval ureter. A case diagnosed preoperatively and treated successfully by a plastic operation. *Br. J. Urol.*, **21**, 209–214.
- Aurell, M., Johnsson, S. and Nilsson, S. (1971). On the quantitation of radiorenograms. *Scand. J. Clin. Lab. Invest.*, **28**, 291.
- Bratt, C. G., Aurell, M., Granerus, G. *et al.* (1983). Late results of pyeloplasty for idiopathic hydronephrosis in adults. *Scand. J. Urol. Nephrol.*, **17**, 329–335.
- Bratt, C. G., Aurell, M. and Nilsson, S. (1977). Renal function in patients with hydronephrosis. *Br. J. Urol.*, **49**, 249–255.
- Culp, O. S. (1961). Choice of operation for ureteropelvic obstruction: review of 385 cases. *Can. J. Surg.*, **4**, 157–161.
- Djurhuus, J. C., Nerström, B. and Rask-Andersen, H. (1976). Dynamics of upper urinary tract in man. Perioperative electrophysiological findings in patients with manifest or suspected hydronephrosis. *Acta Chir. Scand. (Suppl.)*, **472**, 49–58.
- Gosling, J. A. and Dixon, J. S. (1978). Functional obstruction of the ureter and renal pelvis. A histological and electron microscope study. *Br. J. Urol.*, **50**, 145–152.
- Murnaghan, G. F. (1957). Experimental investigation of the dynamics of the normal and dilated ureter. *Br. J. Urol.*, **29**, 443–449.
- Murnaghan, G. F. (1958a). Experimental aspects of hydronephrosis. *Br. J. Urol.*, **31**, 370–376.
- Murnaghan, G. F. (1958b). The dynamics of the renal pelvis and ureter with reference to congenital hydronephrosis. *Br. J. Urol.*, **30**, 321–329.
- Poulsen, E. U., Jørgensen, T. M., Taagehøj-Jensen, F. *et al.* (1987). The functional outcome of Anderson-Hynes pyeloplasty for hydronephrosis. *Scand. J. Urol. Nephrol.*, **21**, 213–217.
- Roberts, M., Slade, N. and Jeffery, P. (1972). Late results in the management of primary pelvic hydronephrosis. *Br. J. Urol.*, **44**, 15–18.
- Sunderland, H. (1963). A review of experiences with the Anderson-Hynes plastic operation for hydronephrosis. *Br. J. Urol.*, **35**, 1–101.
- Tveter, K. J., Nerdrum, H. J. and Mjelnerød, O. K. (1975). The value of radioisotope renography in the follow up of patients operated upon for hydronephrosis. *J. Urol.*, **114**, 680–683.

The Authors

- S. S. Mikkelsen, MD, Registrar, Department of Surgery.
 B. D. Rasmussen, MD, Physiologist, Department of Clinical Physiology and Nuclear Medicine.
 T. M. Jensen, MD, Radiologist.
 W. Hanghøj-Petersen, MD, Head of Department of Clinical Physiology and Nuclear Medicine.
 P. O. Christensen, MD, Head of Department of Surgery.

Requests for reprints to: S. S. Mikkelsen, Pilegaardsvej 155, DK-8361 Hasselager, Denmark.

Renal Carcinoma in Patients Undergoing Nephrectomy: Analysis of Survival and Prognostic Factors

A. P. SENE, L. HUNT, R. F. T. McMAHON and R. N. P. CARROLL

*Department of Urology and Faculty of Medicine Computational Group, Manchester Royal Infirmary;
Department of Pathology, University of Manchester, Manchester*

Summary—A series of 155 patients who underwent nephrectomy for renal carcinoma between 1965 and 1985 at Manchester Royal Infirmary were analysed for survival in relationship to presenting features, surgical staging and histopathology. Univariate and multivariate analyses were carried out. Five-year survival estimates for stage 1 disease were 81%, for stage 2 disease 65%, for stage 3 disease 39% and for stage 4 disease 6%. An erythrocyte sedimentation rate (ESR) greater than 30 mm/h was associated with worse survival and a history of hypertension was associated with better survival. Renal vein invasion alone was related to worse survival. Perinephric fat invasion was also associated with worse survival and this association in the multivariate analysis was more significant than expected, suggesting that the principles of radical surgery should be observed. The presence of granular cells as opposed to clear cells worsened survival. Patients with papillary tumours had a better survival than those with solid tumours.

Renal carcinoma has an incidence of approximately 4/100,000 (Ritchie and Chisholm, 1983) and accounts for 3% of all malignancies. It was described as early as 1826 and yet its natural history remains unpredictable and poorly understood. In 1883 Grawitz described the condition when he noted the striking gross resemblance of the yellow renal tumour to the adrenal cortex, and he suggested that it might be derived from adrenal rests. It was, however, later confirmed by light and electron microscopy that it arises from renal tubular epithelium.

Knowledge of features of the disease which relate accurately to prognosis and survival could be helpful in management. Although systemic therapy has in the past been disappointing, new trials may provide effective adjuvant therapy in the near future. It would be important to be able to select patients who would benefit from such treatment, which may itself have significant side effects.

In this study, 155 patients who underwent nephrectomy for renal carcinoma and had a minimum of 5 years' potential follow-up were analysed statistically to identify features of prognostic significance. We assessed symptoms and signs, surgical staging and histopathology and attempted to relate them to the outcome.

Patients and Methods

The records of 155 patients who underwent nephrectomy for renal carcinoma between 1965 and 1985 were examined. Clinical features at presentation, surgical staging, histopathology and outcome were recorded. When patients died at home or at another hospital, the mode of death was ascertained from the General Practitioners' records or from the other hospital's records.

Of the 155 patients, 152 had unilateral tumours and the classification of Robson *et al.* (1969) was used to stage these patients:

Stage 1—tumour is confined to renal parenchyma and the true capsule is not breached.

Stage 2—tumour invades perinephric fat but is contained within Gerota's fascia.

Stage 3—tumour involves renal vein, inferior vena cava or lymph nodes.

Stage 4—distant metastatic disease or local direct spread is present.

This classification is a modification of the first staging system introduced by Flocks and Kadesky in 1958. In addition, the Stage 3 patients were subdivided into Stage 3A (venous invasion alone), Stage 3B (venous invasion and perinephric fat invasion) and Stage 3C (lymph node involvement). Most patients underwent radical nephrectomy (defined as early ligation of the renal artery and vein and removal of the entire perinephric fat without incising Gerota's fascia). Surgery was accomplished through a flank incision ($n=58$) or by an anterior transperitoneal approach ($n=97$). The operative records indicate that the procedure was modified according to the surgical findings. Visibly enlarged nodes were removed but formal retroperitoneal lymphadenectomy was not performed. Peri-operative deaths were defined as deaths occurring within 1 month of surgery.

Histopathology

The tissue was fixed in 10% neutral buffered formalin and was routinely embedded in paraffin. Haematoxylin and eosin stained sections were examined (mean 3 sections, range 1–11) and analysed according to the parameters defined by Fuhrman *et al.* (1982).

Nuclear grade was determined on the highest grade/most malignant area regardless of quantity. Grade 1 tumours contained small uniform nuclei, approximately 10 μm in dimension, with absent or inconspicuous nucleoli (Fig. 1A). Grade 2 tumours had larger nuclei with irregular outlines, approximately 15 μm in diameter, and nucleoli when examined under high power (Fig. 1B). Grade 3 tumours had cells which were larger again, with irregular nuclei up to 20 μm in diameter and containing nucleoli which were visible on low power microscopy (Fig. 1C). Grade 4 tumours had all of the characteristics of grade 3 lesions but with the addition of bizarre multilobed nuclei and clumped chromatin (Fig. 1D).

Cell type was divided into 3 categories—clear cell (Fig. 1A), granular (dark) cell (Fig. 1B) or mixed. Where more than 75% of the tumour was of either clear or granular type, the tumour was assigned to that group. If the minority component

was greater than 25%, the tumour was classified as of mixed type.

The tumour patterns included (i) solid forms composed of monotonous sheets of cells (Figs 1A and B), (ii) papillary where cells were present lining fibrovascular stalks (Fig. 1C) and (iii) spindle where areas of spindle cell or sarcomatoid differentiation were identified (Fig. 1D). The papillary pattern was assigned only to those tumours where more than 50% of the tumour contained definite fibrovascular stalks.

Histological demonstration of invasion of the renal vein at the hilar resection margin, renal capsular spread, pelvicaliceal invasion and lymph node metastases formed the basis of the surgical staging used to classify the 152 patients with unilateral disease.

Statistical methods

Details from each patient were put on to coding forms for statistical analysis using BMDP (Dixon, 1985) and SAS User's Guide (1985) implemented on the University of Manchester's mainframe computer. Associations between surgical stage and presenting features and histopathological features were assessed using chi-squared tests, after appropriate recombination of cells with small expected frequencies. Univariate survival analysis was carried out by calculating Kaplan-Meier survival estimates and comparing estimates between subgroups of patients using the Logrank test (Peto *et al.*, 1977). The end-point for analysis was death due to renal carcinoma or post-operative death. Deaths from causes other than renal carcinoma were censored in the analysis. Finally, multivariate survival analysis was carried out using the Cox Proportional Hazards regression model. In this analysis any non-significant variables were deleted in a backward-stepwise manner, using the likelihood-ratio test and a 5% level of significance.

Results

Presenting features

Of 155 patients who underwent nephrectomy for renal carcinoma there were 102 males and 53 females (ratio approx 2:1). The age range was 19 to 86 years (median 59). There were 3 patients with bilateral carcinomas and 152 with unilateral disease, 85 on the left and 67 on the right. The weight of the nephrectomy specimens ranged from 90 to 2300 g (median 361). Of 152 patients undergoing nephrectomy for unilateral disease, 69 (45%) had

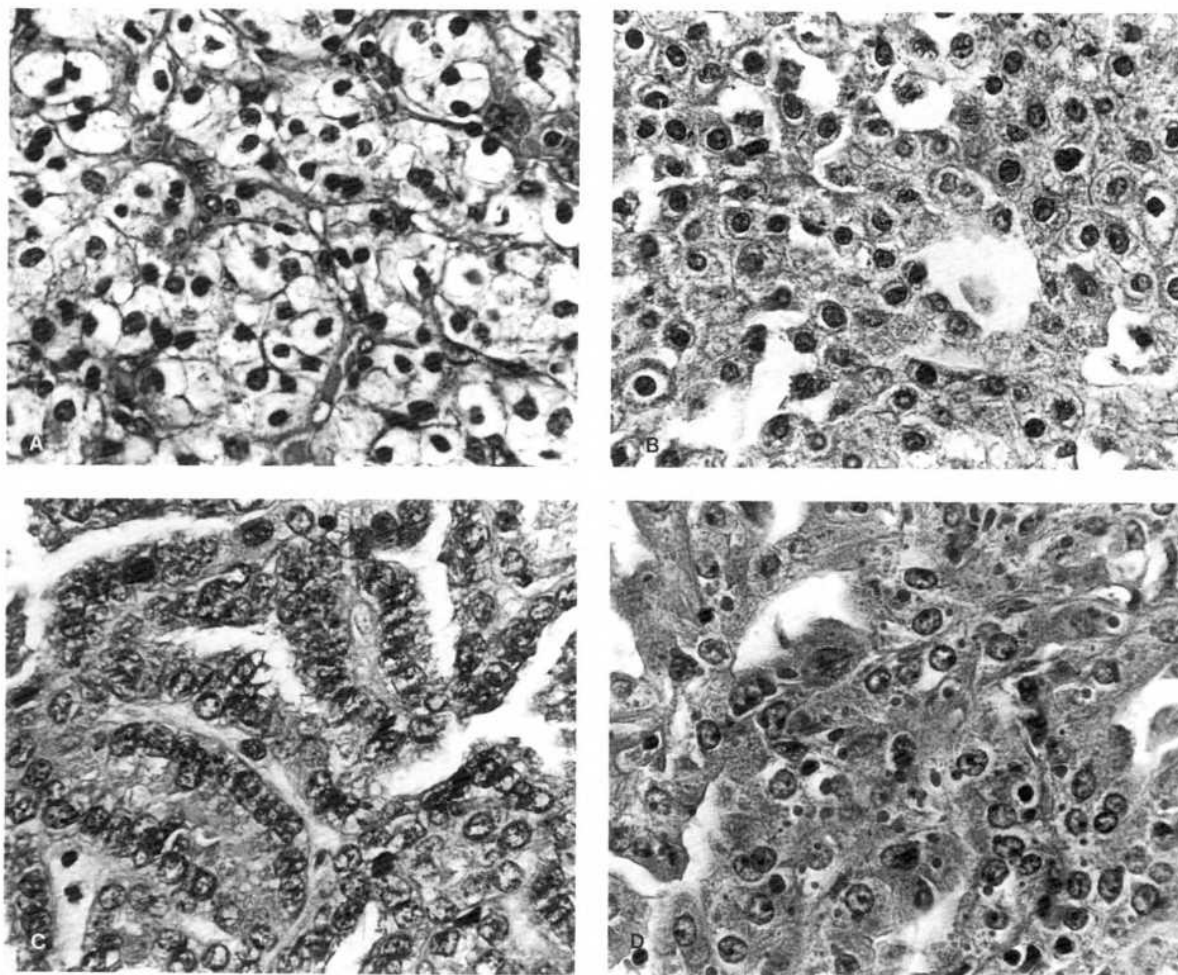


Fig. 1 (A) Classical renal clear cell carcinoma of solid pattern with nuclear grade 1. (H and E $\times 400$). (B) Solid renal granular cell carcinoma with nuclear grade 2. (H and E $\times 400$). (C) Papillary renal granular cell carcinoma with nuclear grade 3. (H and E $\times 400$). (D) Granular renal carcinoma with a solid/spindle cell pattern, nuclear grade 4 and abundant hyaline globules. (H and E $\times 400$).

Stage 1 disease, 15 (10%) Stage 2, 37 (24%) Stage 3 and 31 (20%) Stage 4 disease. Of the 37 patients with Stage 3 disease, 17 were in Stage 3A (venous invasion only), 11 were in Stage 3B (venous and perinephric fat invasion) and 9 were in Stage 3C (nodal involvement). Of the 28 patients with venous invasion 20 had macroscopic and 8 had microscopic involvement.

Table 1 illustrates the incidence of clinical features at presentation for all 152 patients with unilateral disease and according to surgical staging. As expected, haematuria, abdominal mass and pain were the commonest features but the classical triad was present in only 12%. Symptoms of malaise, weight loss or anorexia were present in 30%; 15%

of patients were on antihypertensive treatment at presentation and this had to be continued after surgery. The chi-squared tests indicated significant associations between the presence of malaise, weight loss or anorexia, ESR > 30 mm/h or anaemia (Hb < 10 g/dl in females, < 12 g/dl in males) and increasing surgical stage. Polycythaemia (Hb > 18 g/dl in males, > 16.5 g/dl in females) at presentation occurred in only 3 patients. Hypercalcaemia (calcium > 2.6 mmol/l) without bony metastases occurred in only 2 patients. Abnormal liver function tests were present in only 5 patients but the investigation results were located in only 20 patients. Five patients presented with metastases without haematuria, abdominal pain or an abdom-

Table 1 Features at Presentation of 152 Patients with Unilateral Renal Carcinoma

Stage	Haematuria (%)	Mass (%)	Pain (%)	Classical triad (%)	Pyrexia (%)	Malaise, weight loss or anorexia (%)	Hypertension (%)	Anaemia (%)	ESR > 30 mm/h (%)
1 (n = 69)	50 (73)	27 (39)	31 (45)	5 (7)	7 (10)	12 (17)	12 (17)	12 (17)	16 (23)
2 (n = 15)	8 (53)	8 (53)	8 (53)	0 (0)	0 (0)	4 (27)	3 (20)	5 (33)	4 (27)
3 (n = 37)	30 (81)	17 (46)	16 (43)	6 (16)	7 (19)	13 (35)	6 (16)	15 (41)	22 (60)
4 (n = 31)	16 (52)	19 (61)	15 (48)	7 (23)	3 (10)	16 (52)	2 (7)	14 (45)	22 (71)
All stages (n = 152)	104 (68)	71 (47)	70 (46)	18 (12)	17 (11)	45 (30)	23 (15)	46 (30)	64 (42)
Significance	$P < 0.05$	NS	NS	$P < 0.025^*$	NS	$P < 0.01$	NS	$P < 0.025$	$P < 0.001$

* Stages 1 + 2, 3 + 4 combined.

inal mass. Six patients with carcinomas were diagnosed on routine medical examination. There were no cases of von Hippel-Lindau syndrome.

Clinical course and staging

The follow-up period ranged from surgery until death or up to 20 years (median 4 years). Of the 152 patients with unilateral tumours there were 4 peri-operative deaths (an overall operative mortality rate of 2.6%) and 70 (46%) died of renal carcinoma; of these, 57 (38%) died of carcinoma within 2 years, 8 (5%) between 2 and 5 years and 5 (3%) after 5 years. Sixteen patients (11%) died of unrelated causes; 62 (41%) are still alive at least 5 years after surgery but 2 have recurrent disease.

Stage 1 (tumour confined to renal parenchyma). Of 69 patients, 10 died of disease within 2 years, 2 between 2 and 5 years and 2 after 5 years. There was 1 peri-operative death and 10 patients died of unrelated causes; 44 patients are alive after at least 5 years but 1 has recurrent disease.

Stage 2 (perinephric fat invasion). Of 15 patients, there was 1 peri-operative death, 3 died of disease within 2 years, 1 between 2 and 5 years and 1 after 5 years; 3 died of unrelated causes. There are 6 patients alive after at least 5 years, all disease-free.

Stage 3 (venous or nodal involvement). Of 17 patients in Stage 3A (venous invasion only), 7 died of disease within 2 years, 2 died of disease after 2 years and there was 1 unrelated death at 7 years. Seven are alive and disease-free after at least 5 years. Of 11 patients in Stage 3B (venous and perinephric fat invasion), 4 died of disease within 2 years, 3 died of disease after 2 years and there were 2 unrelated deaths. Two are alive at present and disease-free. Of 9 patients in Stage 3C (lymph node involvement), 6 died of disease within 2 years, 1 died of

disease at 6 years, 1 is alive at 5 years with disease and 1 is disease-free at 9 years.

Stage 4. Of 31 patients there were 2 peri-operative deaths (an operative mortality rate of 6.5%); 27 died of disease within 2 years, 1 died of disease after 5 years and there is 1 disease-free survivor at 17 years. Nineteen patients were known to have distant metastases at presentation and 17 (including 5 with distant metastases) were found to have local invasion at surgery. Within this group there was 1 remarkable case of spontaneous regression. A 49-year-old male presented with haematuria, weight loss, a painful left-sided renal carcinoma and at least 9 pulmonary metastases on chest X-ray. He underwent a left radical nephrectomy, making an uneventful recovery, and the 700 g specimen showed evidence of renal vein invasion. At 3 months the chest X-ray was unchanged but at 8 months it was completely normal. He remains alive and well at 17 years with no evidence of disease.

Bilateral carcinomas

There were 3 patients (1.9%) with bilateral carcinomas whose tumours are not included in the statistical analysis. A 42-year-old male presented with a right-sided carcinoma, having had a left radical nephrectomy for carcinoma 6 years previously. He underwent right radical nephrectomy and was maintained on peritoneal dialysis but he died of uraemia and chronic peritonitis 3 years later. An unfit 62-year-old male presented with synchronous carcinomas and underwent a palliative left nephrectomy. He died 2 years later of disseminated disease. The most fascinating case was a 50-year-old female who presented with a history of abdominal pain, weight loss and a huge left-sided renal carcinoma. She underwent left radical nephrectomy and made an uneventful recovery. Histology confirmed a well encapsulated multifocal renal

carcinoma. She was well until she presented at 7 years with another huge abdominal mass. CT scan confirmed a right-sided multifocal renal carcinoma, but after angiographic studies partial nephrectomy was not deemed appropriate. She did not develop metastases and remained well, although the mass increased in size and she developed chronic anaemia and backache. She died of heart failure secondary to mitral valve disease 6 years after the diagnosis of the second carcinoma. At post mortem a 1100 g, multifocal, well encapsulated right renal carcinoma was found with no evidence of spread.

Histopathology

Tables 2, 3, 4 and 5 illustrate according to surgical staging the cell type, nuclear grading, tumour pattern and the presence of pelvicaliceal invasion respectively. Tumour cell type varied with stage (Table 2), but there was a progressive increase in the percentage of mixed cell tumours and a decrease in the percentage of clear cell tumours as the stage progressed. There was a progressive decrease in the percentage of tumours with nuclear grades 1 and 2 and a corresponding increase in the percentage of tumours with nuclear grade 4 as the staging progressed (Table 3). The decrease in percentage of papillary tumours contrasted with the increase in percentage of spindle cell tumours as the staging progressed (Table 4). Invasion of the collecting system was also more common with increasing

stage (Table 5). The relationship between cell type and nuclear grading is illustrated in Table 6. There was higher nuclear grading in the granular and mixed cell tumours and lower nuclear grading in the clear cell tumours.

Statistical analysis

Univariate survival analysis

Figure 2 illustrates the Kaplan-Meier survival curve for the whole group and in Figure 3 the group is subdivided according to stage. For the whole group, the Kaplan-Meier estimates of survival at 5 and 10 years were 54 and 49% respectively. At 8 years, 56 patients were still alive and none of these died subsequently of renal carcinoma. For stage 1, 5- and 10-year survival estimates were 81 and 77% respectively; for stage 2, 65 and 57% respectively; for stage 3, 39 and 35% respectively; for stage 4, 6 and 3% respectively. The 4 curves differ significantly (Logrank test $P < 0.001$).

In Table 7 the patients were subdivided according

Table 2 Cell Type and Staging

Stage	Clear cell (%)	Granular cell (%)	Mixed cell (%)
1	45 (65)	20 (29)	4 (6)
2	10 (67)	4 (27)	1 (7)
3	22 (60)	9 (24)	6 (16)
4	13 (42)	9 (29)	9 (29)
All stages	90 (59)	42 (28)	20 (13)

Chi-squared test $P < 0.005$ (combining Stages 1 and 2, and 3 and 4).

Table 3 Fuhrman's Nuclear Grading and Staging

Stage	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
1	3 (4)	29 (42)	15 (22)	22 (32)
2	2 (13)	4 (27)	5 (33)	4 (27)
3	0 (0)	5 (14)	8 (22)	24 (65)
4	0 (0)	2 (7)	7 (23)	22 (71)
All stages	5 (3)	40 (26)	35 (23)	72 (47)

Chi-squared test $P < 0.001$ (combining nuclear grades 1 and 2)

Table 4 Tumour Pattern and Staging

Stage	Solid (%)	Papillary (%)	Spindle (%)
1	52 (75)	16 (23)	1 (1)
2	12 (80)	3 (20)	0 (0)
3	28 (76)	5 (14)	4 (11)
4	28 (90)	2 (7)	1 (3)
All stages	120 (79)	26 (17)	6 (4)

Chi-squared test $P < 0.01$ (combining Stages 1 and 2, and 3 and 4).

Table 5 Invasion of Pelvicaliceal System and Staging

Stage	Present (%)
1	19 (28)
2	4 (27)
3	16 (43)
4	23 (74)
All stages	62 (41)

Chi-squared test $P < 0.001$.

Table 6 Cell Type and Fuhrman's Nuclear Grading

Cell type	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	All grades (%)
Granular	0 (0)	4 (10)	9 (21)	29 (69)	42 (100)
Clear	5 (6)	35 (39)	24 (27)	26 (29)	90 (100)
Mixed	0 (0)	1 (5)	2 (10)	17 (85)	20 (100)

Chi-squared test $P < 0.001$ (combining nuclear grades 1 and 2).

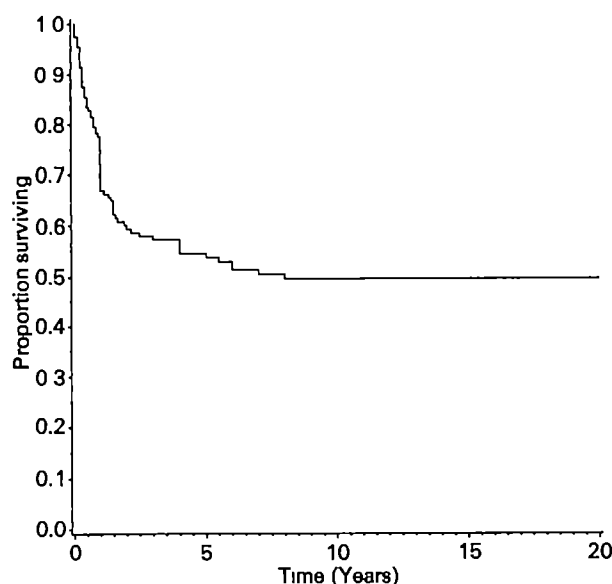


Fig. 2 Survival curve for 152 patients with unilateral renal carcinoma

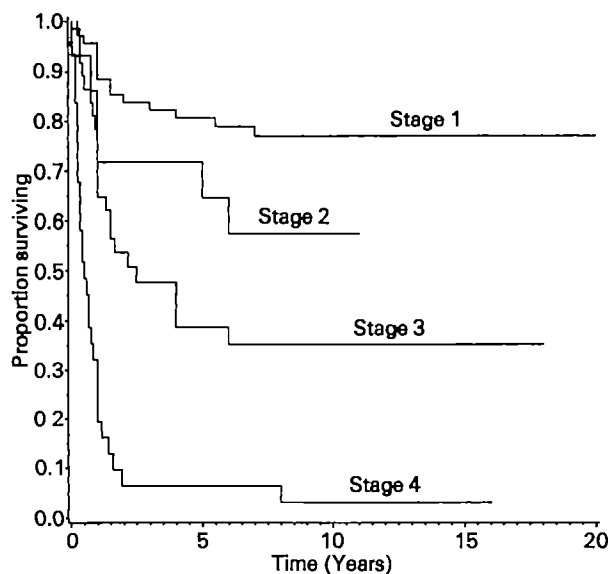


Fig. 3 Survival curves for 69 patients with Stage 1 disease, 15 with Stage 2, 37 with Stage 3 and 31 with Stage 4 disease

to each variable in turn and the survival curves of the subgroups compared. The continuous variables, namely age and weight, were divided into 4 arbitrary intervals (age >50 years, 50–59, 60–69, >70 ; weight of nephrectomy specimen <250 g, 250–399, 400–699, >700). Variables which were statistically significantly related (Table 7) to a worse

Table 7 Univariate Survival Analysis

<i>Log rank test</i>	
<i>Variables</i>	
Age	Not significant
Sex	Not significant
Side	Not significant
Weight	$P < 0.01$
<i>Symptoms</i> (presence or absence of)	
Mass	$P < 0.05$
Haematuria	Not significant
Pain	Not significant
Fever	$P < 0.001$
Weight loss, anorexia or malaise	$P < 0.001$
Hypertension	$P < 0.005$
Anaemia	$P < 0.001$
ESR > 30 mm/h	$P < 0.001$
<i>Histopathology</i>	
Nuclear grade	$P < 0.001$
Cell type	$P < 0.001$
Tumour pattern	$P < 0.001$
Invasion of pelvicaliceal system	$P < 0.005$

survival were increased weight of kidney, mass, fever, the presence of malaise, anorexia or weight loss, anaemia, and ESR > 30 mm/h. The non-significant variables were age, sex, side of tumour and the presence or absence of haematuria or pain. Patients who gave a history of hypertension had a better survival rate than those who did not.

Amongst the histopathological variables, increased nuclear grade, invasion of the collecting system and increased surgical stage were significantly related to a worse survival (Table 7). There was a significant difference between the 3 cell types; patients with "mixed" cellularity had the worst survival, whilst those with "clear" had the best and those with "granular" were intermediate in this univariate analysis (Fig. 4). There was a significant difference between the 3 patterns (Table 7); patients with "spindle" had the worst survival, patients with "papillary" the best and "solid" was intermediate. A further analysis excluding patients with "spindle" confirmed the difference between "papillary" and "solid" ($P < 0.005$).

Surgical stage 3 patients were further subdivided into stages 3A, 3B and 3C (17, 11 and 9 patients respectively). The survival of these groups did not differ significantly ($P > 0.05$), although 3C was slightly worse than the other 2 groups. Further analysis showed that those patients with tumour spread only in the renal vein at the hilar resection margin (Stage 3A) did significantly worse than

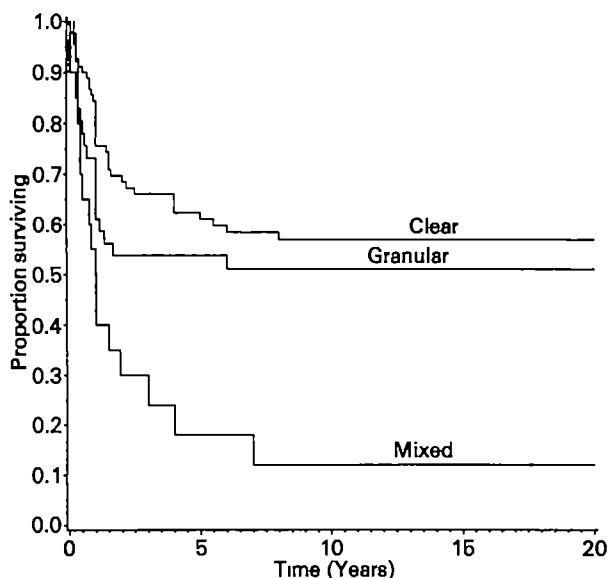


Fig. 4 Survival curves for 90 patients with clear cell carcinomas, 42 with granular cell carcinomas and 20 with mixed cell carcinomas.

patients who had tumour confined to the renal parenchyma (Stage 1) (Fig. 5, $P=0.006$).

There were obvious inter-relationships between the variables; for example, the relationships between stage and presenting symptoms and histopathological classifications have already been noted. We therefore carried out a multivariate

analysis to determine which of the above variables were significantly and independently related to survival.

Multivariate survival analysis

In the multivariate analysis, 2 binary variables (0/1) were used to describe each of the histological variables with 3 categories, *i.e.* "cell type" and "tumour pattern"; baselines (0 for both variables) for analysis were "clear" and "solid" respectively. Three binary variables were created for stage also, taking stage 1 as baseline. The results of the multivariate analysis are shown in Table 8 after deletion of non-significant variables. The variables significantly related to survival were hypertension, $\text{ESR} > 30 \text{ mm/h}$, cell type, pattern and surgical stage. The negative coefficient for hypertension indicated that patients with hypertension fared better with regard to the end-point used, *i.e.* death from renal carcinoma. An $\text{ESR} > 30 \text{ mm/h}$ was conversely related to a worse survival. Both "granular" and "mixed" cell tumours were associated with worse survival than "clear" cell tumours and the coefficients were similar, indicating that the survival was worsened to a similar extent. This is in contrast to the univariate analysis above, where the influences of the other variables were not taken into account. As regards pattern, patients with the "papillary" type fared better than "solid" whilst those with "spindle" were worse. Finally, there was no consistent trend of worsening survival from Stage 1 to Stage 4. Stage 2 patients in this analysis had slightly worse survival than those in Stage 3, as can be seen by the slightly higher coefficient. A further analysis subdivided Stage 3 into 3A, 3B and 3C and all 3 groups were intermediate between Stages 1 and 2 (data not shown).

Discussion

The presenting features of patients, the distribution of patients in the various stages and the histopathology were similar in other retrospective studies (Skinner *et al.*, 1971; Patel and Lavengood, 1978; McNichols *et al.*, 1981; Golimbu *et al.*, 1986).

Survival following nephrectomy for renal carcinoma in the present study was unrelated to age, sex or side of tumour. It was not surprising to find an association between increasing surgical staging and the presence of malaise, weight loss or anorexia, anaemia or an $\text{ESR} > 30 \text{ mm/h}$. The multivariate survival analysis confirmed the confounding effects

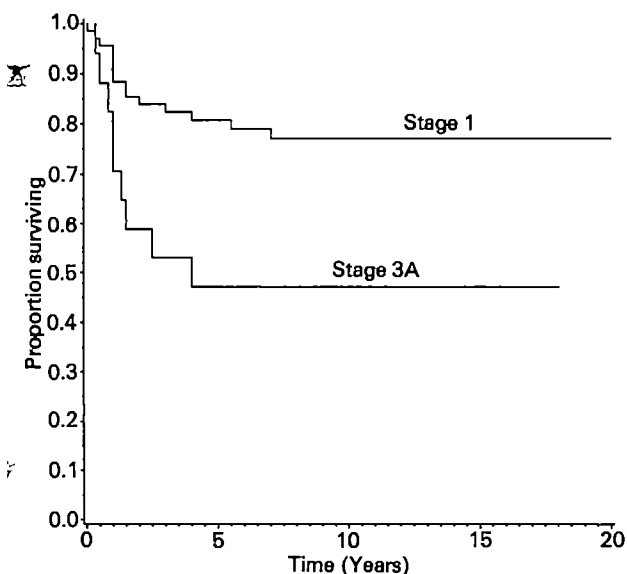


Fig. 5 Survival curves for 69 patients with Stage 1 disease and 17 with Stage 3A disease (renal vein invasion alone).

Table 8 Cox Proportional Hazards Regression Model*

Covariate		Coefficient	(SE)	Significance
Hypertension		-1.3083	(0.5425)	= 0.005
ESR > 30		1.4217	(0.3195)	< 0.001
Cell type	clear (baseline)	0		< 0.05
	granular	0.6923	(0.3106)	
	mixed	0.6380	(0.3120)	
Pattern	solid (baseline)	0		< 0.05
	papillary	-1.0209	(0.4941)	
	spindle	0.4998	(0.5239)	
Stage	1 (baseline)	0	(0.4970)	< 0.001
	2	1.2203	(0.3556)	
	3	0.8317	(0.3659)	
	4	1.6995		

* Cox's Model:

$$\log_e \left(\frac{\lambda(t)}{\lambda_0(t)} \right) = -1.3083 (\text{hypertension}) + 1.4217 (\text{ESR} > 30) \\ + \left\{ \begin{array}{l} 0.6923 (\text{granular}) \\ 0.6380 (\text{mixed}) \end{array} \right\} + \left\{ \begin{array}{l} -1.0209 (\text{papillary}) \\ 0.4498 (\text{spindle}) \end{array} \right\} + \left\{ \begin{array}{l} 1.2203 (\text{Stage 2}) \\ 0.8317 (\text{Stage 3}) \\ 1.6995 (\text{Stage 4}) \end{array} \right\}$$

(All variables were coded No=0 Yes=1).

of these variables, since mass, increased weight of kidney, fever, anaemia and malaise, weight loss or anorexia were no longer significant. The associations between an ESR > 30 mm/h and a worse survival, and between a history of hypertension and a better survival have not previously been reported. Paraneoplastic specific and non-specific syndromes associated with the secretion of substances by the tumour into the circulation have previously been reported (Ritchie and Chisholm, 1983) and this may explain the high ESR often found at presentation. It is interesting to note that those patients who presented on antihypertensive therapy continued to require therapy after nephrectomy and fared better in the analysis, but the reason for this is unclear.

The 5-year and 10-year survival rates for the different stages are similar to those in other retrospective studies. There has been considerable controversy in the North American retrospective studies as to whether or not renal vein invasion alone worsens the prognosis. There is a strong correlation between venous ingrowth and the presence of metastases in post mortem studies (Hellsten *et al.*, 1981). Some studies concluded that venous invasion was associated with decreased survival (Myers *et al.*, 1968; Robson *et al.*, 1969; Patel and Lavengood, 1978) but in these series other factors such as perinephric fat invasion or

nodal involvement were not taken into account. McNichols *et al.* (1981), however, analysed a series of 120 patients with renal vein invasion alone and reported a 55% 5-year survival rate compared with 67 and 65% in patients with Stage 1 and Stage 2 disease respectively. Myers *et al.* (1968) showed that venous invasion was more closely related to survival during the first 2 years after nephrectomy and that once this critical period was passed, survival appeared to be determined by something other than venous invasion. The present series supports the view that renal vein invasion alone is associated with worse survival. Other series (Golimbu *et al.*, 1986), however, showed that renal vein invasion alone did not alter survival and the authors concluded that it represented merely a reflection of the natural growth and biological behaviour of these tumours rather than a significant prognostic factor. They also concluded that it was a combination of renal vein and perinephric fat invasion that decreased survival.

Our multivariate analysis suggests that perinephric fat invasion alone (Stage 2 disease) may worsen the prognosis to an extent similar to that of renal vein invasion alone or lymph node involvement (Stage 3 disease). This has not been reported previously. As a renal carcinoma penetrates into perinephric fat it acquires parasitic blood vessels and lymphatics from adjacent structures. The

tumour may then metastasise to retroperitoneal nodes at a distance from the renal hilum (Hulten *et al.*, 1969). Distant nodes, such as axillary or inguinal nodes, may be shown to contain tumour without involvement of regional nodes (Hellsten *et al.*, 1983). This is one of the reasons why formal retroperitoneal lymphadenectomy is not generally performed in the United Kingdom and may explain disappointing results after lymphadenectomy (DeKernion, 1980). It follows that nodal micrometastases may occur when perinephric fat invasion is present as the tumour acquires parasitic lymphatics. Lymph node involvement in renal carcinoma has been associated with local recurrence, again suggesting an association between perinephric fat invasion and early lymphatic invasion (DeKernion *et al.*, 1978). This association may explain the poorer prognosis we have found in patients with perinephric fat invasion.

Radical nephrectomy involves early control of the vascular pedicle and removal of the kidney in an intact Gerota's fascia. This technique was introduced as early as 1949 (Chute *et al.*, 1949) and Robson *et al.* (1969) further outlined the principles of radical surgery. The tendency for renal carcinoma to extend into the perinephric fat and the apparent increased propensity to lymphatic invasion justify advocating the continuance of these principles. Survival rates of patients with lymph node metastases have generally been poor. Golimbu *et al.* (1986) reported a 17% 5-year survival and a 5% 10-year survival rate. Our series of 9 patients (Stage 3C) showed a 5-year survival of 33% with no survivors at 10 years. On multivariate analysis this group, as with Stages 3A and 3B, showed intermediate survival between Stage 1 and Stage 2. In view of the small numbers in these groups it would be interesting if a larger series confirmed these findings.

In patients with clinical metastatic disease the role of nephrectomy continues to be questioned. Palliative nephrectomy for the relief of intractable symptoms such as pain and haematuria is justifiable. Renal carcinoma has the second highest reported incidence of spontaneous regression of metastases (surpassed only by melanoma) and this has been advanced as justification for nephrectomy in Stage 4 disease (Chisholm, 1975; Freed, 1977). Spontaneous regression of metastases after nephrectomy has been said to occur in 0.8% of cases (Montie *et al.*, 1977) but it is a poorly understood phenomenon, since regression has been reported without nephrectomy (Holland, 1973) and also after radiotherapy (Freed *et al.*, 1977). In the present

series there was one remarkable case of spontaneous regression in an adult male with 9 pulmonary metastases who is alive and well at 17 years. Some reviews conclude that nephrectomy offers no advantage in survival (Middleton, 1967) and others show improved survival only in patients with bony metastases (Johnson *et al.*, 1975; Montie *et al.*, 1977). Further reviews are necessary to identify differences in the quality of survival between surgical and non-surgical groups in Stage 4 disease. Our peri-operative mortality rate in Stage 4 disease was 6.5%; some patients appeared to obtain useful palliation with surgery, whereas others did not. The role of nephrectomy in the presence of metastases remains controversial.

While it is difficult to compare absolutely the histological data in various studies, we have attempted to follow the criteria described by Fuhrman *et al.* (1982) on nuclear grade, cell type and tumour pattern. Our study confirms that granular cell tumours are associated with a worse outcome, as has also been shown by other groups (Skinner *et al.*, 1971), although some later reports are equivocal (McNichols *et al.*, 1981). Fuhrman *et al.* (1982) suggested that granular cell tumours reflected nuclear grade, but they based their conclusions on a comparison between clear and granular cell tumours without referring to surgical staging or nuclear grading. In our univariate analysis (Fig. 3), patients with mixed tumours fared less well than those with clear cell or granular cell tumours. However, patients in surgical Stages 3 and 4 had more mixed cell tumours than patients in surgical Stages 1 and 2 (Table 2). Our multivariate analysis suggested a poorer prognosis associated with the presence of granular cells when taking into account other variables including surgical staging. Higher metastatic rates with granular cell tumours have also been reported (Fuhrman *et al.*, 1982). Our study reveals a better prognosis for papillary tumours and is in agreement with other reviews (Boczko *et al.*, 1979; Waters and Richie, 1979). Other reports are less clear in that they appear to suggest a poorer prognosis for this tumour type (Fuhrman *et al.*, 1982; Schechter and Silverman, 1985; Medeiros *et al.*, 1988). The current study demonstrates a worse prognosis for spindle cell tumours and other reports of this variable appear to substantiate this finding (Skinner *et al.*, 1971; Waters and Richie, 1979; Fuhrman *et al.*, 1982). Nuclear grade, independent of other variables, is not related to survival, but clearly nuclear grading is related to surgical staging (Table 3).

In conclusion, the findings of our multivariate analysis are that of the presenting features an ESR >30 mm/h carries a poor prognosis. In a small number of patients requiring antihypertensive therapy before and after surgery there appeared to be a better prognosis. The staging system defined by Robson *et al.* (1969) is useful, but we have shown that it is helpful to separate patients in Stage 3 into patients with venous invasion alone, those with venous and perinephric fat invasion and those with nodal involvement. Our multivariate analysis suggests that perinephric fat invasion is a very important variable in determining survival and in the circumstances the principles of radical surgery for renal carcinoma are justified. The multivariate analysis allows us to state that patients with clear cell tumours do better than those with granular cell tumours. This information gleaned from the multivariate analysis may be of assistance to clinicians in planning adjuvant therapy.

Acknowledgements

We thank Mrs Sheila Woods, Department of Clinical Studies, Trafford General Hospital, for typing the manuscript and Miss Margaret Banton, Department of Pathological Sciences, University of Manchester, for her help with the photography. We also thank Mr T. Moore and Mr E. Charlton Edwards for granting us permission to include their patients in this study.

References

- Boczko, S., Fromowitz, F. and Bard, R. (1979). Papillary adenocarcinoma of kidney, a new perspective. *Urology*, **14**, 491–495.
- Chisholm, G. D. (1975). Management of metastatic renal carcinoma. *Proc. R. Soc. Med.*, **68**, 775–777.
- Chute, R., Soutter, L. and Kerr, W. S., Jr. (1949). The value of the thoracoabdominal incision in the removal of kidney tumors. *N. Engl. J. Med.*, **241**, 951–960.
- DeKernion, J. B. (1980). Lymphadenectomy for renal cell carcinoma. *Urol. Clin. North Am.*, **7**, 697–703.
- DeKernion, J. B., Ramming, K. P. and Smith, R. B. (1978). The natural history of metastatic renal cell carcinoma: a computer analysis. *J. Urol.*, **120**, 148–152.
- Dixon, W. J. (1985). *BMDP Statistical Software Manual*. Berkeley, London. University of California Press.
- Flocks, R. H. and Kadesky, M. C. (1958). Malignant neoplasms of the kidney: an analysis of 353 patients followed for five years or more. *J. Urol.*, **79**, 196–201.
- Freed, S. Z. (1977). Nephrectomy for renal cell carcinoma with metastases. *Urology*, **9**, 613–616.
- Freed, S. Z., Halperin, J. P. and Gordon, M. (1977). Idiopathic regression of metastases from renal cell carcinoma. *J. Urol.*, **118**, 538–542.
- Fuhrman, S. A., Lasky, L. C. and Limas, C. (1982). Prognostic significance of morphologic parameters in renal cell carcinoma. *Am. J. Surg. Pathol.*, **6**, 655–663.
- Golmbu, M., Joshi, P., Sperber, A. *et al.* (1986). Renal cell carcinoma: survival and prognostic factors. *Urology*, **27**, 291–302.
- Hellsten, S., Berge, T. and Linell, F. (1983). Clinically unrecognized renal carcinoma: aspects of tumour morphology, lymphatic and haematogenous metastatic spread. *Br. J. Urol.*, **55**, 166–170.
- Hellsten, S., Berge, T. and Wehlin, L. (1981). Unrecognised renal cell carcinoma: clinical and pathological aspects. *Scand. J. Urol. Nephrol.*, **8**, 273–278.
- Holland, J. M. (1973). Cancer of the kidney—natural history and staging. *Cancer*, **32**, 1030–1042.
- Hultom, L., Rosencrantz, M., Seeman, T. *et al.* (1969). Occurrence and localization of lymph node metastases in renal carcinoma. *Scand. J. Urol. Nephrol.*, **3**, 129–133.
- Johnson, D. E., Kaesler, K. E. and Samuels, M. L. (1975). Is nephrectomy justified in patients with metastatic renal carcinoma? *J. Urol.*, **114**, 27–29.
- McNichols, D. W., Segura, J. W. and DeWeerd, J. H. (1981). Renal cell carcinoma: long-term survival and late recurrence. *J. Urol.*, **126**, 17–23.
- Medeiros, L. J., Gelb, A. B. and Weiss, L. M. (1988). Renal cell carcinoma—prognostic significance of morphologic parameters in 121 cases. *Cancer*, **61**, 1639–1651.
- Middleton, R. G. (1967). Surgery for metastatic renal cell carcinoma. *J. Urol.*, **97**, 973–977.
- Moatie, J. E., Stewart, B. H., Straffon, R. A. *et al.* (1977). The role of adjunctive nephrectomy in patients with metastatic renal cell carcinoma. *J. Urol.*, **117**, 272–275.
- Myers, G. H., Fehrenbaker, L. G. and Kelalis, P. P. (1968). Prognostic significance of renal vein invasion of hypernephroma. *J. Urol.*, **100**, 420–423.
- Patel, N. P. and Lavengood, R. W. (1978). Renal cell carcinoma: natural history and results of treatment. *J. Urol.*, **119**, 722–726.
- Peto, R., Pike, M. C., Armitage, P. *et al.* (1977). Design and analysis of randomised clinical trials that required prolonged observations of each patient. II. Analysis and examples. *Br. J. Cancer*, **35**, 1–39.
- Ritchie, A. W. S. and Chisholm, G. D. (1983). The natural history of renal carcinoma. *Semin. Oncol.*, **10**, 390–400.
- Robson, C. J., Churchill, B. M. and Anderson, W. (1969). The results of radical nephrectomy for renal carcinoma. *J. Urol.*, **101**, 297–301.
- SAS User's Guide: Statistics. Version 5. (1985). Cary: SAS Institute Inc.
- Schechter, D. J. and Silverman, M. L. (1985). Papillary adenocarcinoma of the kidney: an analysis of 35 cases. *Cancer*, **61**, 1639–1651.
- Skinner, D. G., Colvin, R. B., Vermillion, C. D. *et al.* (1971). Diagnosis and management of renal cell carcinoma. A clinical and pathological study of 309 cases. *Cancer*, **28**, 1165–1177.
- Waters, W. and Richie, J. (1979). Aggressive surgical approach to renal cell carcinoma: review of 130 cases. *J. Urol.*, **122**, 306–309.

The Authors

A. P. Sene, FRCS, Senior Surgical Registrar, Trafford General Hospital, Manchester.

L. Hunt, PhD, MIS, Lecturer, Faculty of Medicine Computational Group, Manchester Royal Infirmary.

R. F. T. McMahon, BSc, MB, MRCP, Lecturer in Pathology, Honorary Consultant Pathologist, University of Manchester.

R. N. P. Carroll, FRCS, FRCSE, Consultant Urologist, Manchester Royal Infirmary.

Requests for reprints to: R. N. P. Carroll, Department of Urology, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL.

Blood Transfusion and Survival Following Surgery for Renal Carcinoma

T.-H. EDNA, K. VADA, F. HESSELBERG and O. K. MJØLNERØD

Department of Surgery, Innherred Hospital, Levanger; Section of Urology, Department of Surgery, University Hospital, Trondheim, Norway

Summary—The effect of peri-operative blood transfusion on survival after surgery for renal carcinoma was studied in 201 patients. In addition to blood transfusion, several other factors were included in a multivariate analysis. Using Cox's proportional hazards model, transfusion of more than 4 units of blood was found to be an independent prognostic factor in addition to tumour stage, erythrocyte sedimentation rate and macrohaematuria.

Peri-operative blood transfusion has been reported to have a detrimental effect on survival following surgery for cancer. This may be due to the immunosuppressive effect of blood transfusion. Using multivariate analysis, the independent prognostic effect of transfusion has been studied. A negative effect on survival has been reported for prostate cancer (Heal *et al.* 1988; McClinton *et al.*, 1990), colorectal cancer (Voogt *et al.*, 1987; van Lawick van Pabst *et al.*, 1988), lung cancer (Moores *et al.*, 1989), cervical cancer (Blumberg *et al.*, 1988) and osteosarcoma (Chesi *et al.*, 1989). Others have found no independent effect on survival in colorectal cancer (Nathanson *et al.*, 1985), gastric cancer (Kampschoer *et al.*, 1989), lung cancer (Keller *et al.*, 1988) and breast cancer (Voogt *et al.*, 1987).

Few studies have been done on the effect of blood transfusion on survival in renal carcinoma. A possible negative effect was reported by Mikulin *et al.* (1986) and Moffat and Sunderland (1985) but no such effect was found by Manyonda *et al.* (1986) and Moffat *et al.* (1987). We have studied survival in a larger series of patients after surgery for renal carcinoma, to determine the effect of transfusion in relation to other risk factors.

Patients and Methods

The records of 68 patients operated on for renal carcinoma at Innherred Hospital between 1969 and 1987 and 133 patients treated at the Regional Hospital of Trondheim between 1974 and 1987 were reviewed.

The series included 108 men and 93 women whose median age at operation was 64 years (range 27–82). Information on peri-operative transfusion was gathered, together with data on known and possible risk factors such as age, sex, haemoglobin and erythrocyte sedimentation rate (ESR) on admission, microscopic or macroscopic haematuria, loin pain, pre-operative plugging of the renal artery, duration of operation, tumour stage and tumour size. Retrospective staging was assessed using the Robson classification (Robson *et al.*, 1969).

The vital status was known in all cases. Eight patients whose cause of death was uncertain were considered to have died from a disease not related to renal carcinoma. Those who died from causes other than renal carcinoma, or who survived until the end of the study, were treated as censored data. Adjusted survival rates were calculated by using death from renal carcinoma as the terminal event and death from an unrelated cause as a censored event.

The patients were divided into 3 groups. Group I received no transfusion during their hospital stay. Group II were given between 1 and 4 units of blood and group III received more than 4 units. Adjusted survival times for the groups were compared using the Kaplan-Meier product-limit method. The survivor functions across the 3 groups were compared using the log-rank (Mantel-Cox) test. An altered trend in survivor function with increasing units of blood transfusion was tested using the trend version of the Mantel-Cox and Breslow tests (Benedetti *et al.*, 1990).

To investigate the combined effects of different variables on survival, Cox's proportional hazards regression model was used (Hopkins, 1990). The event of interest was death from renal carcinoma. At first, all possible prognostic factors (except blood transfusion) were used. The significant factors were selected by a backward stepwise approach. To test whether the variable "transfusion" made a statistically significant improvement, this was added to the model as the last step of the analysis.

Results

In the course of the study 120 patients (60%) died; 91 deaths were related to renal carcinoma.

Blood transfusions were given to 154 patients (77%). The median amount transfused was 2 units (range 1–21). The median age at operation was 64 years (range 27–82).

Survival after operation is shown in the Figure. At 30 months the total number of patients at risk was 108 and at 60 months it was 68. In testing the univariate relationship between transfusion and survival, the difference between groups I and II was not significant. Group III was different from groups I and II ($P < 0.0001$, log rank test). Groups II and III taken together were different from group I ($P < 0.02$). There was an overall trend towards decreasing survival with increasing volumes of total blood transfusion (Mantel-Cox and Breslow trends $P = 0.0001$).

In the multivariate model using Cox's proportional hazards regression, the previously described baseline factors were tested. A stepwise backward approach was used to select the factors which together were significantly associated with time to cancer-related death (Table 1). The significant factors were tumour stage, ESR and macrohaematuria. Patients with macrohaematuria fared better than those without.

Finally, the variable "peri-operative blood transfusion" was added to the model. This had an

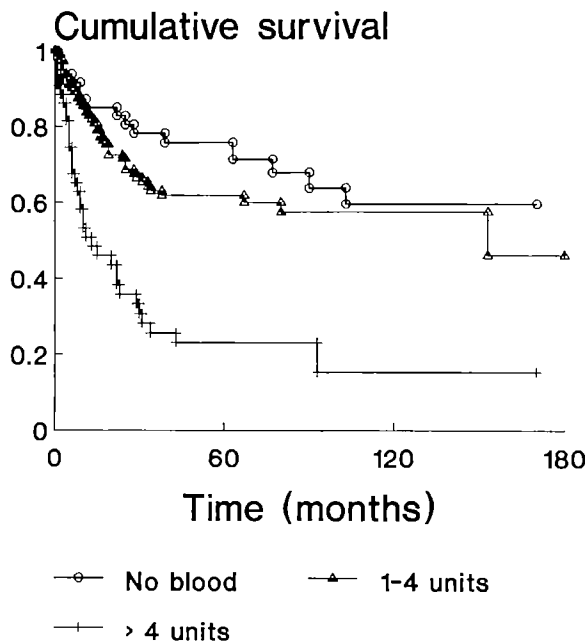


Fig. Kaplan-Meier life tables of cumulative survival following surgery for renal carcinoma in patients given 0, 1–4 and >4 units of blood.

additional significant effect when more than 4 units of blood were considered (Wald test $P = 0.005$) (Table 1).

Table 2 shows the 2-year cumulative survival in relation to stage and transfusion status. Very few patients with tumour stage 4 survived 2 years. The 1-year cumulative survival for these patients was 0.26 when 0 to 4 units of blood had been given and 0.08 when more than 4 units had been given.

During the first half of the study period whole blood was transfused. During the latter years packed red cells were used. When analysis was limited to the years when only whole blood was used the effect of blood transfusion on survival was unchanged.

Discussion

The major determinant of survival was tumour stage. Macrohaematuria was associated with improved survival rates (Moffat *et al.*, 1987). A causal relationship is unlikely and the explanation may be an association between macrohaematuria and an unmeasured prognostic variable. In patients with macrohaematuria the tumours might have been discovered earlier.

The seemingly marked effect of transfusion on survival which was shown in the univariate analysis

Table 1 Survival Analysis using Cox's Proportional Hazards Model

Variable	No of patients	No. of cancer-related deaths (%)	Relative hazard	95% confidence limits
Stage 1	79	19 (24)	1 (ref)	
2	38	14 (37)	1.69	0.85-3.38
3a	35	15 (43)	1.71	0.84-3.49
3b	8	5 (63)	5.30	1.91-14.75
3c	5	5 (100)	5.59	1.81-17.28
4	36	33 (92)	9.90	5.28-18.56
ESR <40	104	33 (32)	1 ref	
>40	97	58 (60)	2.14	1.35-3.40
Macrohaematuria: No	118	62 (53)	1 (ref)	
Yes	83	29 (35)	0.63	0.39-1.02
Transfusion: 0-4 units	158	58 (37)	1 (ref)	
>4 units	43	33 (77)	2.01	1.23-3.28

A relative hazard value greater than 1 indicates a negative effect on survival time. A value less than 1 has the reverse interpretation.

Table 2 Two-year Cumulative Survival in Relation to Stage and Transfusion Status

Stage	Transfusion (units)	No of patients	No. of cancer-related deaths (%)	Cumulative survival at 2 years
1	0-4	73	16 (22)	0.90
1	>4	6	3 (50)	0.83
2	0-4	35	12 (34)	0.79
2	>4	3	2 (67)	0.67
3	0-4	27	10 (37)	0.70
3	>4	21	15 (71)	0.34
4	0-4	23	20 (87)	0.18
4	>4	13	13 (100)	0.08

diminished, but was still significant when viewed in the light of the other prognostic factors selected in Cox's multivariate analysis.

Larger tumours with increasingly difficult operations may have a worse prognosis and increase the need for transfusion. The size and stage of the tumour were tested in the multivariate analysis. Difficult operations would be partly reflected in the longer duration of the procedure, a factor which was taken into account in the analysis. Although unmeasured variables might have confounded the analysis, peri-operative transfusion of more than 4 units appeared to have an independent negative effect on survival.

Transfusion of more than 4 units seemed to have an adverse affect on cumulative survival at 2 years for all tumour stages. However, one must be careful not to draw firm conclusions regarding stages 1 and 2, since few of these patients received more than 4 units of blood.

Wobbes *et al.* (1989) found a relationship between the volume of blood given and survival in colorectal carcinoma. Significant differences were found in the disease-free survival rate if more than 6 units of blood were given.

A dose-dependent relationship between transfusion and negative effect on survival has also been reported after resection of colorectal liver metastases (Stephenson *et al.*, 1988). Patients receiving more than 10 units of blood had a significantly decreased overall survival rate than patients who received 3 to 10 units.

The immunosuppressive effect of transfusion has been proposed as a reason for the effect on survival in cancer patients. Lieberman *et al.* (1990) showed that transfusion of washed red cells induced deficits in cellular immunity and resulted in diminished host survival in a murine neuroblastoma model. The effect was present when allogeneic blood was transfused but absent in syngeneic transfusions.

A deleterious effect of transfusion on tumour recurrence may also be mediated by the increased mitogenic activity observed in stored blood (Hoh *et al.*, 1990). The principal changes occurred from the end of the second week. Increased mitogenic activity was measured in cancer patients following the transfusion of stored blood.

In conclusion, peri-operative blood transfusion seems to have a moderate, adverse effect on survival in patients undergoing surgery for renal carcinoma. The practical implication is that peri-operative transfusion should be given only when absolutely essential. In particular, precautions should be taken during the operation to avoid major haemorrhage, since this could necessitate the transfusion of multiple units of blood.

References

- Benedetti, J., Yuen, K. and Young, L. (1990). Life tables and survivor functions. In *BMDP Statistical Software Manual*, ed. Dixon, W. J., Brown, M. B., Engelman, L. *et al.* Pp. 739–768. Berkeley, Los Angeles, Oxford: University of California Press.
- Blumberg, N., Agarwal, M. M. and Chuang, C. (1988). A possible association between survival time and transfusion in cervical cancer. *Yale J. Biol. Med.*, **61**, 493–500.
- Chesti, R., Cazzola, A., Bacci, G. *et al.* (1989). Effect of perioperative transfusions on survival in osteosarcoma treated by multimodal therapy. *Cancer*, **64**, 1727–1737.
- Heal, J. M., Chuang, C. and Blumberg, N. (1988). Perioperative blood transfusions and prostate cancer recurrence and survival. *Am. J. Surg.*, **156**, 374–380.
- Hoh, H., Umpleby, H. and Taylor, I. (1990). Recurrence of colorectal cancer and perioperative blood transfusion. Is blood storage time important? *Dis. Colon Rectum*, **33**, 127–130.
- Hopkins, A. (1990). Survival analysis with covariates. In *BMDP Statistical Software Manual*, ed. Dixon, W. J., Brown, M. B., Engelman, L. *et al.* Pp. 769–806. Berkeley, Los Angeles, Oxford: University of California Press.
- Kampschoer, G. H., Maruyama, K., Sasako, M. *et al.* (1989). The effects of blood transfusion on the prognosis of patients with gastric cancer. *World J. Surg.*, **13**, 637–643.
- Keller, S. M., Groshen, S., Martini, N. *et al.* (1988). Blood transfusion and lung cancer recurrence. *Cancer*, **62**, 606–610.
- Lieberman, M. D., Shou, J., Sigal, R. K. *et al.* (1990). Transfusion-induced immunosuppression results in diminished host survival in a murine neuroblastoma model. *J. Surg. Res.*, **8**, 498–503.
- Manyonda, I. T., Shaw, D. E., Foulkes, A. *et al.* (1986). Renal cell carcinoma: blood transfusion and survival. *Br. Med. J.*, **293**, 537–538.
- McClintor, S., Moffat, L. E., Scott, S. *et al.* (1990). Blood transfusion and survival following surgery for prostatic carcinoma. *Br. J. Surg.*, **77**, 140–142.
- Milkuln, T., Powell, C. S., Urwin, G. H. *et al.* (1986). Relation between blood transfusion and survival in renal adenocarcinoma. *Br. J. Surg.*, **73**, 1036–1037.
- Moffat, L. E. F., Sunderland, G. T. and Lamont, D. (1987). Blood transfusion and survival following nephrectomy for carcinoma of kidney. *Br. J. Urol.*, **60**, 316–319.
- Moffat, L. E. F. and Sunderland, G. T. (1985). Relation between recurrence of cancer and blood transfusion. *Br. Med. J.*, **291**, 971.
- Moore, D. W., Plantadosi, S. and McKneally, M. F. (1989). Effect of perioperative blood transfusion on outcome in patients with surgically resected lung cancer. *Ann. Thorac. Surg.*, **47**, 346–351.
- Nathanson, S. D., Tilley, B. C., Schultz, L. *et al.* (1985). Perioperative allogeneic blood transfusions. Survival in patients with resected carcinomas of the colon and rectum. *Arch. Surg.*, **120**, 734–738.
- Robson, C., Churchill, B. and Anderson, W. (1969). The results of radical nephrectomy for renal cell carcinoma. *J. Urol.*, **101**, 297–301.
- Stephenson, K. R., Steinberg, S. M., Hughes, K. S. *et al.* (1988). Perioperative blood transfusions are associated with decreased time to recurrence and decreased survival after resection of colorectal liver metastases. *Ann. Surg.*, **208**, 679–687.
- van Lawick van Pabst, W. P., Langenhorst, B. L., Mulder, P. G. *et al.* (1988). Effect of perioperative blood loss and perioperative blood transfusions on colorectal cancer survival. *Eur. J. Cancer Clin. Oncol.*, **24**, 741–747.
- Voogt, P. J., van der Velde, C. J., Brand, A. *et al.* (1987). Perioperative blood transfusion and cancer prognosis. Different effects of blood transfusion on prognosis of colon and breast cancer patients. *Cancer*, **59**, 836–843.
- Wobbes, T., Joosen, K. H. G., Kuypers, H. H. C. *et al.* (1989). The effect of packed cells and whole blood transfusions on survival after curative resection for colorectal carcinoma. *Dis. Colon Rectum*, **32**, 743–748.

The Authors

T.-H. Edna, MD, PhD, Consultant Surgeon.
 K. Vada, MD, Senior Registrar.
 F. Hesselberg, MD, Chief Consultant, Section of Urology, Department of Surgery, Innherred Hospital.
 O. K. Mjølnerød, MD, Chief Consultant, Section of Urology, Department of Surgery, University Hospital of Trondheim.

Requests for reprints to: T.-H. Edna, Department of Surgery, Innherred Hospital, N-7600 Levanger, Norway.

Ureteric Complications of Renal Transplantation

S. H. KASHI, J. P. A. LODGE, G. R. GILES and H. C. IRVING

University Department of Surgery and Department of Radiology, St James's University Hospital, Leeds

Summary—Of 507 consecutive recipients of renal allografts, 45 developed a urological complication. In 39 patients (7.7%) ureteric problems were implicated and these comprised 30 cases of obstruction and 9 cases of ureteric necrosis presenting as urinary leakage.

In 7 patients ureteric obstruction resolved following a period of nephrostomy decompression; 10 patients were reconstructed surgically and this was successful in 8, with 2 patients requiring further surgical procedures. Ten patients were successfully treated by percutaneous stenting after dilatation of the stricture. Stenting failed in 4 patients and in 1 patient caused rupture of a calix. All 10 stents have now been removed and there is no recurrence of stricture (follow-up 32.0 ± 8.6 months). Of the remaining 3 grafts, 2 were removed and the other graft had percutaneous removal of a ureteric calculus.

The 1-year survival rate of allografts in the ureteric complication group was 84.6%; in the recipients without a urological complication it was 81%.

It was concluded that an active approach to ureteric problems following renal transplantation results in the rescue of the majority of allografts.

Ureteric complications of renal transplantation have been reported in 5 to 12.5% of renal transplants (Anderson *et al.*, 1972; Salvatierra *et al.*, 1977; Smolev *et al.*, 1977; Mundy *et al.*, 1981; Hunter, 1986). It is essential that these complications are diagnosed early and differentiated from rejection, which is the commonest cause of deterioration in allograft function. Delay in accurate diagnosis and inappropriate anti-rejection therapy may result in the loss of the transplanted kidney and is also associated with increased morbidity and mortality (Weil *et al.*, 1971; Becker and Kutcher, 1978).

We have reviewed the records of 507 consecutive renal transplants carried out over a 6-year period at St James's University Hospital, Leeds, to record the incidence of ureteric complications in the era since the introduction of cyclosporin as an immunosuppressive agent and to assess the long-term results of surgical and radiological methods of management.

Patients and Methods

Between January 1984 and April 1990, 507 allografts were transplanted consecutively into 495 patients. The study group consisted of 325 males and 170 females, with 12 patients undergoing 2 transplant procedures. The mean age in the female population was 36.8 years (range 2–67) and 38.6 years (range 3–71) in the male recipients. The right kidney was transplanted in 248 cases and 259 recipients received the left kidney.

Throughout the series the usual technique of urinary tract reconstruction was an internal tunnelled ureteroneocystostomy (transvesical). If the bladder was found to be too small to allow the creation of a submucosal tunnel, an external ureteroneocystostomy (extravesical) was carried out. The extravesical technique involved the creation of a 1-cm cystotomy and direct anastomosis of the ureter to the edge of the bladder mucosa using interrupted 3/0 catgut sutures.

Ureteroneocystostomy was performed on 501 occasions. In 485 operations the transvesical nipple technique was used. The extravesical method was

employed in 16 cases and in 3 patients the allograft ureter was implanted into an ileal conduit. In 3 other cases, owing to special circumstances, continuity of the urinary tract was established using pyeloureterostomy or ureteroureterostomy. Stents or splints were not used in the transvesical group, although 4 of the extravesical anastomoses were stented. Urethral catheter drainage was maintained for at least 5 days in all patients, with the period extended to 7 days in cases where the bladder was considered to be thin-walled or small.

Allograft function was monitored daily with measurement of serum creatinine, urea and electrolytes and daily urine output. Deteriorating renal function was investigated by ultrasonography, isotope renography, renal biopsy or fine needle aspiration cytology as appropriate. At present the recipients at this centre undergo regular ultrasonic examination as a screening procedure with a baseline scan within 3 days after transplantation. Suspected urinary extravasation is investigated by cystography followed by antegrade pyelography under ultrasound guidance if further information is required. Suspected ureteric obstruction is investigated by antegrade pyelography and in doubtful cases pressure flow studies are undertaken to clarify the significance of a radiologically demonstrated narrowing.

Cyclosporin monotherapy was administered to all transplant recipients initially in a dose of 15 mg/kg/day in 2 divided doses and the dose adjusted to reduce plasma cyclosporin level to the therapeutic range for the assay used and presently to less than 1200 ng/ml. Latterly, the plasma cyclosporin level has been estimated every third day using Abbotts TDX system (Abbotts Diagnostics Ltd) by a fluorescent competition technique with polyclonal antisera. In patients with pre-formed cytotoxic antibodies the immunosuppressive therapy was altered to triple therapy with azathioprine 1 mg/kg, prednisolone EC 0.3 mg/kg and cyclosporin 6–10 mg/kg.

Statistical analysis of the results was performed using the χ^2 test and the Mann-Whitney U test with correction for large numbers.

Results

Thirty-five episodes of ureteric obstruction were demonstrated by antegrade pyelography in 30 transplants. Of the 15 patients who presented with a urinary leak, 9 were found to have developed ureteric necrosis and in 6 cases the leaks came from the bladder closure. The true overall incidence of

ureteric problems in the study group was, therefore, 7.7% (39 patients). Factors which may affect ureteric healing were analysed for each of the 2 populations (no urological complication and ureteric complication) but there was no obvious correlation with any factors other than delayed primary function of the graft for the first 5 post-transplant days (Table 1).

In 21 patients the site of ureteric obstruction was a stricture at the vesicoureteric junction and in 5 transplants mid to distal ureteric stenosis impeded urine flow. The other cases comprised idiopathic pelviureteric junction obstruction (1), external compression of renal pelvis by tumour (1), calculus obstruction (1), and obstruction at the pyeloureterostomy (1).

Ureteric obstruction was managed in the earlier part of the study by preliminary insertion of a percutaneous nephrostomy catheter followed by surgical reimplantation. Eight of the 10 surgical procedures were successful but 2 patients required further surgery. In 1 case the stricture persisted after a second procedure involving per-operative dilatation of the stenosed section but was successfully treated with percutaneous balloon dilatation and placement of a double-pigtail stent (Medi-Tech Inc, Watertown, USA). Two transplant nephrectomies were carried out in the group with ureteric obstruction because of a lymphoma compressing the renal pelvis in 1 patient and arterial thrombosis in the other. The obstruction resolved spontaneously in 7 allografts after a period of nephrostomy catheter drainage.

Of 14 more recent patients, 10 have been successfully treated with dilatation of the stricture and insertion of a double-pigtail ureteric stent after nephrostomy drainage had allowed recovery of renal function. However, stenting failed in 4 transplants because of the presence of a long, tight stricture in the ureter (1), technical difficulties in gaining satisfactory access to an upper pole calix (2) and the rupture of a calix on guide wire manipulation (1). All of these allografts were salvaged with surgical reconstruction.

All recipients with a ureteric double-pigtail stent were placed on low dose co-trimoxazole and regularly examined ultrasonically to ensure satisfactory drainage was continued. Two patients have been treated for bacterial urinary infection and 2 other recipients have suffered urinary *Candida* spp. infection. One of these patients required ureteric reimplantation because the stent was blocked with fungal growth. All of the percutaneously placed stents in the patients included in this series were

Table 1 Donor and Recipient Data

		No. of complications (n=468)	Ureteric problems (n=39)
Recipient	Age (years)	37.8 ± 15	40.7 ± 14
	M:F	2.0:1	1.5:1
Donor	Age (years)	32.4 ± 15	40.7 ± 16
	M:F	1.3:1	2.0:1
Kidney	L:R	1.05:1	1.2:1
	No. of Arteries	1	76.2%
		2	20.2%
Panel Reactive Antibody		≥3	3.6%
		0%	81.0%
		≤50%	13.0%
Total no. of mismatch loci		≤100%	6.0%
		0	4.7%
		1-2	42.0%
		3-4	49.5%
		5-6	3.8%
Storage time (h)	20.4 ± 6.5	18.9 ± 4.8	
Type Of Perfusion	E/Collins	9.2%	8.0%
	HOC	70.0%	72.0%
	PBS 140	15.4%	20.0%
	Others	5.4%	
Fluid	Others	5.4%	0.0%
Delayed function*	24.0%	46.0%	
Rejection episodes	1.18 ± 1.5	1.46 ± 1.2	

Values are mean ± standard deviation.

Percentages are for the total in each group.

*($P=0.005$, χ^2 test).

removed cystoscopically at 3 to 6 months and there has been no evidence of recurrence of the strictures with a mean follow-up period of 32.0 months (SD ± 8.6 months).

It is our practice to allow for the recovery of renal function before attempting percutaneous or surgical treatment of urological complications. This was achieved by percutaneous placement of a nephrostomy catheter under ultrasound guidance as the initial treatment. Following placement of a nephrostomy (n=21), the median serum creatinine decreased from 485 to 396 $\mu\text{mol/l}$ at 48 h and the improvement continued to provide a median serum creatinine level of 229 $\mu\text{mol/l}$ 2 weeks after intervention (Fig.).

Of the 9 patients with lower ureteric/vesicoureteric junction urinary leakage, 5 underwent surgical procedures, 1 resolved on continued bladder catheter drainage and 2 transplants were managed with the placement of a double-pigtail stent across the site of leakage. One graft was lost in this group owing to overwhelming sepsis.

Table 2 summarises graft survival and median and interquartile ranges for serum creatinine for

those grafts presenting a ureteric complication and the allografts without a urological complication. There was no difference in graft survival at 12 months; however, renal function was significantly worse in the transplants with a ureteric problem ($P=0.01$). The success of aggressive management of ureteric complications is demonstrated by Table 3, which indicates a 12-month graft survival rate of

Table 2 Graft Survival and Serum Creatinine at 12 Months (all kidneys)

	Graft survival (%)	Serum creatinine ($\mu\text{mol/l}$)
Ureteric complication (n=39)	84.6	175 (135-197) (n=33)
No ureteric complication (n=468)	81	139 (106-163) (n=375)

Values for serum creatinine are median with interquartile ranges for allografts surviving at 12 months. ($P=0.01$, Mann-Whitney U test).

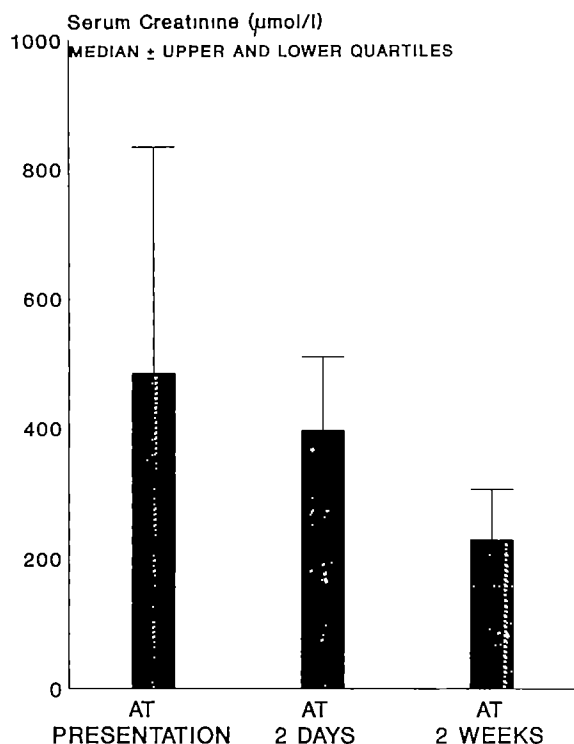


Fig. Serum creatinine following nephrostomy catheter drainage.

100% in the stented group and 87% in those managed surgically. Both methods, however, failed to reverse the damage suffered by the allograft during the period of obstruction, as shown by the higher median serum creatinine at 12 months when compared with that of the non-complicated grafts.

Discussion

In this series of 507 consecutive renal transplanta-

tions the incidence of ureteric complications was 7.7%, with ureteric obstruction at the vesicoureteric junction the commonest complication (4.7%). The cause of ureteric stenosis or necrosis remains uncertain, although the blood supply of the terminal ureter is clearly vulnerable as it is entirely derived from the main renal artery. Although there has been speculation that unwanted vasoactivity associated with the use of cyclosporin might be associated with increased ureteric problems, a ureteric complication rate of 7.7% using cyclosporin is little different from the 10% reported by Mundy *et al.* (1981) in 1,000 patients transplanted in the pre-cyclosporin period. In addition, there is no evidence that multiple renal arteries are associated with increased risk to the ureter, as suggested by Hricko *et al.* (1973). However, necrosis of the distal ureter must be related to vascular insufficiency due either to deficient proximal supply or to the effects on the vasculature by drug action, preservation injury or rejection. Analysis of the data in this series does not indicate a significantly higher number of rejection episodes in those patients with ureteric stenosis or leak, nor are the kidneys transplanted in the patients with pre-formed cytotoxic antibodies more prone to ureteric damage. Similarly, we found no association with the degree of matching on the HLA loci (Table 1). However, delayed primary function was significantly more predominant in the group with ureteric complications, which would suggest that damage during organ harvesting or the preservation period played a definite role ($P=0.005$).

Ultrasonography of renal allografts is highly sensitive for the exclusion of obstruction, as in the absence of pelvicaliceal dilatation the likelihood of ureteric obstruction is very low. Further investiga-

Table 3 12-month Allograft Survival and Function (ureteric complication)

	*No.	Post-op. days on treatment (mean $\pm$ SD)	Graft survival (%)	Serum creatinine (μ mol/l)
Stenting	12	40 $\pm$ 12	100	182 (134–231) (n=12)
Reconstruction	15	27 $\pm$ 5	87	177 (135–317) (n=13)
Nephrostomy/ catheter drainage	8	23 $\pm$ 11	88	172 (95–178) (n=7)

*=Exclusions 3 allograft nephrectomy.

1 percutaneous removal of stone.

Values for serum creatinine are median and interquartile ranges for allografts surviving to 12 months

tion of these recipients with antegrade pyelography to exclude obstruction as a cause of deterioration in graft function is unlikely to be beneficial (Kashi *et al.*, 1991).

In the earlier part of this study the majority of cases of ureteric obstruction were managed surgically. Latterly, however, with our increasing experience of percutaneous techniques, percutaneous dilatation with placement of a double-pigtail stent has become our first line of treatment, thus reducing the morbidity associated with surgical remedial procedures. Neither surgical nor radiological procedures for the treatment of obstruction were attended by graft loss or patient mortality. This compares favourably with other previously reported surgical experience (Smolev *et al.*, 1977; Mundy *et al.*, 1981). We elect to remove the stents after 3 to 6 months, though this may be unduly conservative because it is recognised that in the non-transplant patient population in whom double-pigtail stents had been placed as the primary treatment for urinary leaks, complete ureteric healing was observed within 2 to 7 weeks (Narasimham *et al.*, 1990). Thus there may be a case for removing stents sooner than we have done to date.

It is clear that an aggressive policy of investigation and treatment can significantly reduce patient morbidity and mortality as well as allowing the salvage of the allografts. We recommend that all renal transplant recipients undergo routine ultrasound monitoring of the allograft and that any suspected urological complication is actively and urgently investigated and appropriately treated. Percutaneous placement of a nephrostomy catheter under ultrasound guidance is a simple and effective method which allows recovery of renal function and provides time for further evaluation and formulation of a plan of definitive management. The use of a percutaneously placed ureteric double-

pigtail stent, with or without balloon dilatation of any strictures, has become an acceptable and effective alternative to surgical management.

References

- Anderson, E. E., Glenn, J. F., Stegler, H. F. *et al.* (1972). Ureteral implantation in renal transplantation. *Surg. Gynecol. Obstet.*, 134, 494-496.
- Becker, J. and Kutcher, R. (1978). Urological complications of renal transplantation. *Semin. Roentgenol.*, 13, 341-351.
- Hricko, G. M., Birtch, A. G., Bennett, A. H. *et al.* (1973). Factors responsible for urinary fistula in the renal transplant recipient. *Ann. Surg.*, 178, 609-615.
- Hunter, D. W. (1986). Evaluation and treatment of non-vascular problems of the transplanted kidney. *Semin. Intervent. Radiol.*, 3, 104-114.
- Kashi, S. H., Lodge, J. P. A., Giles, G. R. *et al.* (1991). Ultrasonography of renal allografts: collecting system dilatation and its clinical significance. *Nephrol. Dial. Transplant.*, 6, 358-362.
- Mundy, A. R., Podesta, M. L., Bewick, M. *et al.* (1981). The urological complications of 1000 renal transplants. *Br. J. Urol.*, 53, 397-402.
- Narasimham, D. L., Jacobson, B., Nyman, U. *et al.* (1990). Primary double pigtail stenting as treatment of upper urinary tract leaks. *J. Urol.*, 143, 234-236.
- Salvatierra, O., Olcott, C., Amend, W. J. *et al.* (1977). Urological complications of renal transplantation can be prevented or controlled. *J. Urol.*, 117, 421-429.
- Smolev, J. K., McLoughlin, M. G., Rolley, R. *et al.* (1977). The surgical approach to urological complications in renal recipients. *J. Urol.*, 117, 10-12.
- Well, R., Simmons, R. L., Tallent, M. B. *et al.* (1971). Prevention of urological complications after kidney transplantation. *Ann. Surg.*, 174, 154-160.

The Authors

- S. H. Kashi, FRCSE, Tutor in Surgery.
J. P. A. Lodge, FRCS, Lecturer in Surgery.
G. R. Giles, MD, FRCS, Professor of Surgery.
H. C. Irving, FRCR, DMRD, Consultant Radiologist.

Requests for reprints to: G. R. Giles, Department of Surgery, St James's University Hospital, Beckett Street, Leeds LS9 7TF.

Voiding Dysfunction and Urodynamic Findings in Patients with Cervical Spondylotic Spinal Stenosis Compared with Severity of the Disease

T. L. J. TAMMELA, M. J. HEISKARI and O. A. LUKKARINEN

Division of Urology and Department of Neurosurgery, Oulu University Central Hospital, Oulu, Finland

Summary—A group of 30 consecutive patients (26 men and 4 women, mean age 51 years), with clinically and radiologically verified cervical spondylosis causing radiculopathy and/or myelopathy, were questioned about voiding symptoms, examined urodynamically and subjected to tests of tibial somatosensory evoked potentials (SEP). Seventeen patients (61%) complained of irritative bladder symptoms and detrusor hyperactivity was demonstrated urodynamically in 13 (46%). Three (11%) experienced difficulty in emptying the bladder, and all of these had a hypotonic detrusor. The bladder was insensitive to cold in 36%, this and SEP abnormalities being more common in the patients with clinically severe myelopathy, whereas detrusor hyperactivity was found equally in all patients. Urodynamic investigation seems to provide additional information on the severity of the disease and is therefore recommended for wider use in these patients.

Cervical spondylosis is a generalised disease process affecting all levels of the cervical spine and encompassing a sequence of degenerative changes in the intervertebral discs, osteophytosis of the vertebral bodies, hypertrophy of the facets and laminal arches and ligamentous and segmental instability (Lestini and Wiesel, 1989). Developmental stenosis of the cervical spinal canal predisposes the patient to myelopathy, particularly when associated with cervical spondylosis (Stratford, 1978). In a lateral location, spondylosis causes only radicular findings (Mayfield, 1979; Lunsford *et al.*, 1980a), whereas a paracentral or central location may cause cord compression in addition to the root lesions (Mayfield, 1979). Where this is present the symptoms most commonly occur in the lower extremities, involving disturbance of gait in 50 to 90% of cases (Gregorius *et al.*, 1976; Lunsford *et al.*, 1980b). Spasticity and hyperactive tendon reflexes occur in 50 to 90% of cases (Lunsford *et al.*, 1980b). Lower urinary tract sphincter disturbances have been reported to be quite frequent (Gregorius

et al., 1976; Lunsford *et al.*, 1980b) and bladder dysfunction has been regarded as common, with symptoms of frequency, urgency and urge incontinence (Hald and Bradley, 1982).

It is well known that partial lesions along the spinal cord can affect lower urinary tract function in many ways (Gunasekera *et al.*, 1984), but the literature contains only a few reports in which voiding symptoms and urodynamics have been studied systematically in patients with cervical spondylotic spinal stenosis (Ando, 1990).

Voiding symptoms were examined in patients with clinically and radiologically verified spondylotic spinal stenosis causing radiculopathy and/or myelopathy and the urodynamic findings compared with somatosensory evoked potentials, clinical severity and the duration of the disease.

Patients and Methods

The series comprised 30 consecutive patients (26 men and 4 women aged 30 to 65 years (mean 51)) who were suffering from symptoms of radiculopathy or radiculomyelopathy caused by spondylotic spinal stenosis of the cervical vertebrae. The duration of

symptoms varied from 1 to 120 months (mean 18). The radiculopathy patients suffered mainly from cervical and radicular pain, and reflex disturbances and sensory or motor defects were observed in all of them. The radiculomyelopathy patients exhibited both radiculopathy and abnormal gait, with lower limb spasticity and hyper-reflexia.

The patients were divided into 3 groups according to the severity of the disease. Group I included 6 patients with only radicular symptoms and signs in the upper extremities and with no clinical findings of myelopathy. Group II comprised 11 patients who also had evidence of myelopathy with mild lower limb spasticity and hyper-reflexia with or without difficulty in walking. Group III included 13 patients who suffered from severe radiculomyelopathy with marked spasticity, hyper-reflexia and abnormal gait.

Plain X-ray films of the cervical spine in patients with spondylosis showed degenerative changes, often at multiple levels, particularly narrowing of the disc space with hypertrophic spur formations at the margins of the intervertebral discs and facet joints. Myelography with a positive contrast medium (Amipaque or Omnipaque) showed root and cord compression in all cases, indicating a defect, distortion or narrowing of the contrast medium surrounding the spinal cord. There were also root sleeve abnormalities, most often at several levels (C4-T1). Eight patients showed a complete block and 22 a partial block to the flow of contrast medium within the spinal canal. Computed tomography (CT) was also performed in half of the patients.

Somatosensory evoked potentials (SEP) were recorded following stimulation of the posterior tibial nerves separately behind the medial malleolus with surface electrodes. The stimuli were 0.2 ms square wave electrical pulses with a repetition rate of 5 Hz. The intensity of the stimulus was adjusted to elicit a consistent twitch of the big toe that was not uncomfortable to the patient. The recording electrodes were placed over the popliteal fossa and the scalp at the midline foot area of the sensory cortex. The scalp electrode was referred to linked ears. The frequency response of the amplifier was in the range 2 to 2000 Hz. A total of 500 to 2000 responses from each recording session was averaged by a computer. The analysis time was 200 ms. Measurement of the SEP peak latency (P_2) and the amplitude of the P_2-N_2 from peak to peak over the scalp was carried out by computer cursoring. The formulae for height correction of the latency values were obtained by linear regression analysis. The

controls consisted of 12 healthy men and 8 women ranging in age from 22 to 54 years. The amplitude of P_2-N_2 in the control recording was $4.5 \pm 2.8 \mu V$ and the latency of P_2 40.2 ± 1.9 ms (Heiskari *et al.*, 1988). The SEP findings were graded as normal (SEP grade 0) when the amplitude or latency values were under 2 SD, slightly abnormal (SEP grade I) when they ranged between 2 and 3 SD and markedly abnormal (SEP grade II) when they were over 3 SD.

The patients were asked to provide a symptom score concerning micturition and each patient underwent a urological examination followed by urodynamic studies that included medium-fill water cystometry with and without coughing provocation, pressure-flow electromyography (EMG) using an anal plug electrode and urethral pressure profile measurements using the Brown-Wickham method. Intra-abdominal pressure was recorded through a rectal balloon catheter and electronically subtracted from the intravesical pressure to indicate detrusor pressure. The methods and definitions conformed to the standards proposed by the International Continence Society (Abrams *et al.*, 1988). The patients also underwent a modification of Bors' ice-water test as part of the urodynamic examination to test bladder hyperactivity and sensibility (Tamela *et al.*, 1989).

Results

Two patients (1 from clinical group I and the other from group III) were excluded from the final analysis because urodynamic examination showed an obvious bladder outlet obstruction caused by benign prostatic hyperplasia. They also had obstructive symptoms and an enlarged prostate. Thus the final analysis included 28 patients—24 men and 4 women.

Seventeen patients (61%) had irritative bladder symptoms, including frequency, urgency and urge incontinence, whereas 3 (11%) had difficulty in emptying the bladder. Eight patients (28%) regarded their micturition as normal. Urodynamic examination revealed detrusor hyper-reflexia (contractions > 15 cmH₂O) in 13 patients (46%) and a hypotonic detrusor (no contraction during micturition) in 3 (11%). Detrusor sphincter dyssynergia was not recorded in any of the patients. Maximum urethral closure pressure (mean of 3 consecutive measurements) was 94 ± 35 cmH₂O in the males and 46 ± 8 cmH₂O in the females. The iced water test induced hyper-reflexic detrusor contractions (> 15 cmH₂O) in 7 patients (25%) and sensitivity

Table 1 Micturition Symptoms and Clinical Severity of the Disease

<i>Clinical group</i>	<i>Irritative symptoms</i>	<i>Difficulties in emptying bladder</i>	<i>Normal micturition</i>
I (n=5)	4	0	1
II (n=11)	7	0	4
III (n=12)	6	3	3
Total (n=28)	17	3	8

Table 2 Urodynamic and SEP Findings in Relation to Clinical Severity of the Disease

<i>Clinical group</i>	<i>Hyper-reflexia</i>	<i>Hypotonic detrusor</i>	<i>Normal detrusor</i>	<i>Lack of sensitivity to cold</i>	<i>SEP grade</i>		
					<i>0</i>	<i>I</i>	<i>II</i>
I (n=5)	2	0	3	0	2	3	0
II (n=11)	5	0	6	5	3	3	5
III (n=12)	6	3	3	5	2	0	10
Total (n=28)	13	3	12	10	7	6	15

to cold was lacking in 11 patients (39%). Residual urine was 50 ± 57 ml.

Irritative symptoms occurred with equal frequency in all groups, as did hyper-reflexia (Table 1). Sensitivity to cold was lacking in half of the patients in groups II and III but none in group I. SEP abnormalities were correlated with the degree of the disease (Table 2), most of the abnormal findings being in group III, although SEP abnormalities and a lack of sensitivity to cold were found equally in

the patients with a hyper-reflexic, hypotonic and normal detrusor (Tables 2 and 3). A lack of sensitivity to cold was more common in the patients whose symptoms had been present for more 6 months (Table 4).

Discussion

Most of the patients with radiculopathy or myelopathy caused by cervical spondylosis had symptoms

Table 3 Correlation between Urodynamic Findings and SEP Grade

<i>Detrusor stability</i>	<i>Lack of sensitivity to cold</i>	<i>SEP grade</i>		
		<i>0</i>	<i>I</i>	<i>II</i>
Hyper-reflexia (n=13)	5	4	3	6
Hypotonic detrusor (n=3)	2		1	2
Normal detrusor (n=12)	4	3	2	7
Total (n=28)	11	7	6	15

Table 4 Comparison of Duration of Symptoms with Urodynamic Findings and SEP Abnormalities

<i>Duration of symptoms (months)</i>	<i>Hyper-reflexia</i>	<i>Hypotonic detrusor</i>	<i>Normal detrusor</i>	<i>Lack of cold sensation</i>	<i>SEP grade</i>		
					<i>0</i>	<i>I</i>	<i>II</i>
≤6 (n=12)	6	1	5	3	2	4	6
>6 (n=16)	7	2	7	7	5	2	9
Total (n=28)	13	3	12	10	7	6	15

of lower urinary tract dysfunction. Nearly two-thirds of them complained of irritative bladder symptoms, with detrusor hyperactivity being confirmed urodynamically in 46%. Three patients had difficulty in emptying the bladder and all had a hypotonic detrusor. The urodynamic findings were normal in 43%. Contrary to the observations of Gunasekera *et al.* (1984), who found asymptomatic urinary tract dysfunction in 20% of patients with upper motor neuron lesions identified in a urodynamic examination, all of our patients with abnormal urodynamic findings were also symptomatic.

The reason for detrusor hyperactivity is obviously compression of the inhibitory pathways occupying the reticulospinal tracts which lie superficially in the lateral columns of the spinal cord (Hald and Bradley, 1982). An underactive detrusor is assumed to be accompanied by myelopathy in the posterior funiculus of the cervical cord, which mediates bladder proprioceptive sensation (Ando, 1990). Contrary to previous opinion (Hald and Bradley, 1982), detrusor sphincter dyssynergia was not found to be a problem in these patients.

Although the development of symptomatic myelopathy has been shown to be closely correlated with the degree of anteroposterior narrowing of the canal (Wolf *et al.*, 1956; Payne and Spillane, 1957; Nurick, 1972), ischaemia probably also plays a major role in pathogenesis. Distortion and compression of the small vessels in the cord are of prime importance (Breig *et al.*, 1966; Shimomura *et al.*, 1968; Nurick, 1972) and may explain the inability to feel cold that was often found in our patients with grade II to III myelopathy. Exteroceptive stimuli generated in the urothelium, including temperature, are thought to ascend in the lateral spinothalamic tracts (Bathia and Bradley, 1983). On the other hand, tibial SEP disturbances are known to be closely correlated with posterior column signs, being even more sensitive to posterior column involvement than the clinical examination (Yu and Jones, 1985; Heiskari *et al.*, 1988). Although tibial SEP disturbances and lack of sensitivity to cold occurred mostly in patients with severe disease, there was no clear correlation between these features. This is understandable, since tibial SEPs and the ability to feel cold water in the bladder reflect the functioning of different tracts in the cervical spine. They nevertheless seem to give some additional information on the severity of myelopathy.

Both irritative symptoms and detrusor hyper-reflexia were found in all clinical groups, although normal detrusor function occurred less often in

group III. The fact that some patients with mild disease also showed detrusor hyperactivity is understandable, since spondylotic spinal stenosis tends to affect the ventral part of the spinal cord first and the posterior part later. Detrusor under-activity was clearly associated with severe myelopathy, all 3 patients concerned being in clinical group III and showing abnormalities in the tibial SEP test, while 2 of them were also insensitive to cold. The duration of symptoms had no clear association with the urodynamic or tibial SEP findings except for the inability to feel cold, which was more common in the patients with a longer duration of symptoms. This may be explained by the sensitivity of the spinothalamic tracts to prolonged hypoxia (Breig *et al.*, 1966; Shimomura *et al.*, 1968; Nurick, 1972).

Our results indicate that voiding dysfunction is a common finding in patients with spondylotic cervical spinal stenosis, mostly involving an inhibitory lesion. When performed together with radiological and neurophysiological examination, urodynamic tests may provide additional information on the severity of myelopathy. Its wider use is therefore recommended in these patients.

References

- Abrams, P., Blaivas, J. G., Stanton, S. L. *et al.* (1988). The standardisation of terminology of lower urinary tract function. *Scand. J. Urol. Nephrol. (Suppl.)*, **114**, 5-19.
- Ando, M. (1990) Neurogenic bladder in patients with cervical cord compression disorders *Nippon Hinyokika Gakkai Zasshi.*, **18**, 243-250.
- Bathia, N. N. and Bradley, W. E. (1983). Neuroanatomy and physiology: innervation of the urinary tract. In *Female Urology*, ed Raz, S. Pp. 12-32. Philadelphia Saunders.
- Breig, A., Turaball, I. and Hassler, O. (1966). Effects of mechanical stress on the spinal cord in cervical spondylosis: a study in fresh cadaver material. *J. Neurosurg.*, **25**, 45-56.
- Gregorius, F. K., Estrin, T. and Cramdall, P. H. (1976). Cervical spondylotic radiculopathy and myelopathy. *Arch. Neurol.*, **33**, 618-625.
- Gunasekera, W. S. L., Richardson, A. E., Seneviratne, K. N. *et al.* (1984). Clinical correlation of urodynamic findings in patients with localized partial lesions of the spinal cord and cauda equina. *Surg. Neurol.*, **21**, 148-154.
- Hald, T. and Bradley, W. E. (1982). *The Urinary Bladder. Neurology and Dynamics* Pp. 53 and 163-164. London: Williams and Wilkins.
- Heiskari, M., Tolonen, U., Kovala, T. *et al.* (1988). Somatosensory evoked potentials to posterior tibial nerve stimulation in cervical radiculopathy and radiculomyelopathy. *Neurotop.*, **5**, 78-82.
- Lesttilä, W. F. and Wiesel, S. W. (1989). The pathogenesis of cervical spondylosis. *Clin. Orthop.*, **239**, 69-93.
- Lunsford, L. D., Bissonette, D. J., Jannetta, P. J. *et al.* (1980a). Anterior surgery for cervical disc disease. Part 1: Treatment of lateral cervical disc herniation in 253 cases. *J. Neurosurg.*, **53**, 1-11.

- Lunsford, L. D., Bissonette, D. J. and Zorub, D. S. (1980b). Anterior surgery for cervical disc disease. Part 2: Treatment of cervical spondylotic myelopathy in 32 cases. *J. Neurosurg*, **53**, 12-19.
- Mayfield, F. H. (1979). Cervical spondylotic radiculopathy and myelopathy. In *Advances in Neurology*, ed. Thompson, R. A. and Green, I. R. Volume 22, pp. 307-321. New York: Raven Press.
- Nurick, S. (1972). The pathogenesis of the spinal cord disorder associated with cervical spondylosis. *Brain*, **95**, 87-100.
- Payne, E. E. and Spillane, J. D. (1957). The cervical spine: an anatomicopathological study of 70 specimens using a special technique with particular reference to the problem of cervical spondylosis. *Bram*, **80**, 571-596.
- Shimomura, Y., Hukuda, S. and Mizuno, S. (1968). Experimental study of ischemic damage to the cervical spinal cord. *J. Neurosurg.*, **28**, 565-581.
- Stratford, J. (1978). Congenital cervical spinal stenosis a factor in myelopathy. *Acta Neurochir. (Wien)*, **41**, 101-106.
- Tammela, T., Hellström, P., Kontturi, M. *et al.* (1989). The bladder cooling test as a part of urodynamic investigation. *Neurourol. Urodynam.*, **7**, 425-426.
- Wolf, B., Khilnani, M. and Malik, L. (1956). Sagittal diameter of bony cervical canal and its significance in cervical spondylosis. *J. Mount Sinai Hosp.*, **23**, 283-296.
- Yu, Y. L. and Jones, S. J. (1985). Somatosensory evoked potentials in cervical spondylosis. Correlation of median, ulnar and posterior tibial nerve responses with clinical and radiological findings. *Brain*, **108**, 273-300.

The Authors

- T. L. J. Tammela, MD, PhD, Associate Professor of Urology, Division of Urology.
 M. J. Heiskari, MD, PhD, Neurosurgeon.
 O. A. Lukkarinen, MD, PhD, Assistant Professor of Surgery, Division of Urology.

Requests for reprints to: T. L. J. Tammela, Division of Urology, Department of Surgery, Oulu University Central Hospital, SF-90220 Oulu, Finland.

Acute Urinary Retention. Comparison of Suprapubic and Urethral Catheterisation

A. F. HORGAN, B. PRASAD, D. J. WALDRON and D. C. O'SULLIVAN

Department of Urology, University College and Regional Hospital, Cork, Ireland

Summary—A total of 86 consecutive patients who presented to the accident and emergency department with acute urinary retention due to prostatomegaly required catheterisation; 56 received suprapubic catheters and 30 were catheterised urethrally. Both groups were followed up for 3 years.

Of the 30 patients catheterised urethrally, 12 (40%) developed urinary tract infections compared with 10 (18%) urinary tract infections in the 56 patients catheterised suprapubically. Five patients (17%) in the urethral group developed urethral strictures with no strictures in the suprapubic group. Two patients catheterised urethrally developed epididymo-orchitis and 1 developed septicaemia. None of the patients with suprapubic catheters developed these complications. Furthermore, 16 patients catheterised suprapubically underwent successful trial clamping of their catheter, whereas 7 patients required recatheterisation following removal of their urethral catheters.

We recommend that the use of suprapubic catheters should become the preferred initial treatment for acute urinary retention.

Bladder catheterisation is one of the essential first steps in the treatment of the patient with acute urinary retention. There are associated complications regardless of whether this is performed urethrally or suprapubically. Bacteriuria is an almost inevitable consequence of an indwelling urethral catheter and urethral stricture rates of 43% have been reported following urethral catheterisation (Keitzer *et al.*, 1986), especially with latex catheters. However, despite these facts, urethral catheterisation continues to be the treatment of choice in many units for acute urinary retention. In this hospital in 1985 the policy for catheterising these patients changed from the urethral to the suprapubic route. This gave us the opportunity to follow up 86 consecutive patients who presented to the casualty department with acute retention of urine and to compare the results of urethral versus suprapubic catheterisation.

Patients and Methods

A total of 100 patients was studied. All presented with acute urinary retention. Fourteen of these were due to causes other than prostatomegaly and were therefore excluded, leaving 86 patients in the study. Thirty consecutive patients who were catheterised urethrally were studied and compared with 56 consecutive patients who were suprapubically catheterised. All patients were followed up for 3 years. On admission to the accident and emergency department each patient had a urea and electrolytes determination and was then catheterised by a member of the urology service using an aseptic technique. Those catheterised urethrally had a latex Foley catheter inserted and attached to a closed drainage system. Suprapubic catheterisation was performed using a 12F Cystofix catheter, having first established the presence of a distended bladder by sterile aspiration with a 21 gauge needle. The catheter was sutured to the skin of the abdominal wall with non-absorbable sutures. Prophylactic antibiotics were not routinely used. Catheter speci-

mens of urine were sent for microscopy, culture and sensitivity at initial presentation, at the time of surgery and at variable intervals between. Urinary tract infections were diagnosed if culture after 48 h revealed $\geq 100,000$ colony-forming units/ml of urine.

Results

Eighty-six patients were studied. The mean age was 72 years. The mean duration of prostatic symptoms was 10 months. The mean period of catheterisation was 3 weeks for those with urethral catheters and 5 weeks for those with suprapubic catheters. Of the 30 patients undergoing urethral catheterisation 12 developed urinary tract infections (40%). Five of these had more than 1 infection. In contrast, only 10 of the 56 patients catheterised suprapubically (18%) developed urinary tract infections (chi-squared test, $P < 0.05$) and 3 had more than 1 infection. Two of the patients catheterised urethrally developed epididymo-orchitis and 1 developed a staphylococcal septicaemia. None of the patients catheterised suprapubically developed either of these complications.

The urethral catheter was removed in 11 patients (37%) in an attempt to re-establish micturition. Following this, 7 patients (23%) required recatheterisation owing to recurrent retention. Trial clamping of the suprapubic catheter was attempted in 22 patients (39%). This was successful in 16 (29%) and 7 (13%) did not require subsequent surgery.

Five (17%) of the patients catheterised urethrally subsequently developed urethral strictures. No patient in the suprapubic group developed urethral strictures ($P < 0.01$). In addition, 5 patients who had been urethrally catheterised required a peri-operative Otis urethrotomy. None of these went on to develop urethral strictures during follow-up. Only 1 patient who had been suprapubically catheterised required peri-operative urethrotomy. The average duration of catheterisation of those patients who subsequently developed strictures was 5 days.

The suprapubic catheter became dislodged in 13 patients while awaiting surgery and had to be replaced in 10 of these patients. This complication occurred in only 1 of the patients catheterised urethrally. All complications are shown in the Table.

Surgery was required in 74 of the 86 patients studied; 55 had transurethral resections, 12 had open prostatectomies and 7 had open cystotomy for insertion of a suprapubic catheter because they

Table Complications of Urethral versus Suprapubic Catheterisation

Complication	Urethral (n = 30)	SPC (n = 56)
Urinary tract infection	12 (40)	10 (18)
Stricture	5 (16.7)	0
Epididymo-orchitis	2 (6.7)	0
Septicaemia	1 (3.4)	0
Dislodgement	1 (3.4)	12 (23)

Values in parentheses are percentages.

SPC: suprapubic catheter

were medically unfit for prostatic surgery at the time. These patients were then evaluated and followed up by the appropriate medical service on the understanding that they would undergo prostatic resection when medically fit. Histological examination of the resected prostatic tissue showed 75% to have benign prostatic hyperplasia and 25% to have adenocarcinoma of the gland.

Discussion

With a ratio of 1 urological surgeon per 270,000 population in this region, several weeks usually elapse before definitive prostatic surgery can be undertaken following the onset of acute urinary retention. There is, however, no general agreement in the literature regarding which form of catheter should be used during this period. Urethral catheters are routinely used in many hospitals, with the suprapubic catheter being reserved for those cases where this has failed.

Rates of urinary tract infections up to 67% (Hodgkinson and Hodari, 1966) have been reported in patients with urethral catheters *in situ*. In the post-laparotomy patient a suprapubic catheter has been shown to be associated with significantly fewer infections (Sethia *et al.*, 1987). A number of studies comparing the 2 types of drainage in women following gynaecological surgery have shown a marked preference for the suprapubic route (Shapiro *et al.*, 1982; Hodgkinson and Hodari, 1966; Barham, 1973). Such comparisons have not been made, to our knowledge, regarding the patient presenting with acute urinary retention due to prostatic outflow obstruction.

In the present study, a significant difference in rates of urinary tract infection was found between the suprapubic and urethrally catheterised groups. Bacterial colonisation of catheters occurs quickly and associated morbidity is not uncommon. Extra-

luminal spread of bacteria within the peri-urethral space is probably the major route by which bacteria gain entry to the urinary bladder, as shown by the isolation of the same species of bacteria from both meatal and urine cultures (Garibaldi *et al.*, 1980). Use of the suprapubic catheter should therefore bypass this site of potential colonisation and decrease the incidence of urinary tract infections.

In addition to the difference in the rates of urinary tract infections, we also found a significant difference in the rates of urethral stricture formation between the 2 groups. The incidence of urethral stricture was clearly unrelated to the duration of initial catheterisation. No patient in the suprapubic group developed a urethral stricture. This suggests that it is not the urological procedure itself, but the method of catheterisation prior to this, which is the cause of subsequent stricture formation. The same conclusions were reached in a previous study comparing the post-operative use of suprapubic and transurethral catheters following transurethral resection of the prostate (Hammarsten *et al.*, 1989). The high incidence of stricture formation in the urethrally catheterised group may be partly explained by the fact that latex catheters were used in all cases. There is some evidence to suggest that PVC and Silastic catheters cause less urethral reaction and reduce stricture formation (Blacklock, 1986; Ferrie *et al.*, 1986). One prospective study showed no difference between PVC and latex catheters in the treatment of acute urinary retention but no long-term follow-up was carried out (Allardice *et al.*, 1988).

A further advantage of the suprapubic catheter is the fact that a trial of micturition can be performed without removal of the catheter. It has been shown that such a trial is justified, in that re-establishment of micturition occurs frequently (Taube and Gajraj, 1989), and up to 23% of patients may not require surgery (Murray *et al.*, 1984). In our group of patients with suprapubic catheters, 16 (29%) underwent successful trial clamping and 7 (13%) did not require any surgery. However, in order to perform a trial of micturition in the urethral group it was necessary to remove the catheter. Following this, 7 patients (23%) were subjected to the discomfort of another episode of acute retention and the morbidity associated with the insertion of another urethral catheter.

The only complication that was repeatedly associated with the suprapubic catheter was dislodgement. In all, 13 patients (23%) developed this complication and 11 of these needed to have their catheter replaced. There is an obvious need for a

more secure form of catheter fixation. The insertion of a self-retaining Foley catheter through a suprapubic introducer may lead to more satisfactory results in this regard.

In conclusion, this study has shown that the use of suprapubic catheters in acute urinary retention significantly reduces the risk of urinary tract infection and urethral stricture formation. It also allows for a trial of micturition without the discomfort, the urethral trauma and the risk of infection associated with the re-insertion of a urethral catheter. We recommend that the use of suprapubic catheters should be evaluated widely and, if the present results are substantiated, that this should become the preferred initial treatment for acute urinary retention.

References

- Allardice, J. T., Standfield, N. J. and Wyatt, A. P. (1988). Acute urinary retention: which catheter? *Ann. R. Coll. Surg. Engl.*, **70**, 366-368.
- Barham, K. A. (1973). Suprapubic bladder drainage in gynaecological surgery. *Aust. N. Z. J. Surg.*, **43**, 32.
- Blacklock, N. J. (1986). Catheters and urethral strictures. *Br. J. Urol.*, **58**, 475-477.
- Ferrie, B. G., Groome, J., Sethia, B. *et al.* (1986). Comparison of silicone and latex catheters in the development of urethral stricture after cardiac surgery. *Br. J. Urol.*, **58**, 549-550.
- Garibaldi, R. A., Burke, J. P., Britt, M. R. *et al.* (1980). Meatal colonization and catheter-associated bacteriuria. *N. Engl. J. Med.*, **303**, 316-318.
- Hammarsten, J., Lindqvist, K. and Sunzel, H. (1989). Urethral strictures following transurethral resection of the prostate. The role of the catheter. *Br. J. Urol.*, **63**, 397-400.
- Hodgkinson, C. P. and Hodari, A. A. (1966). Trochar suprapubic cystostomy for postoperative bladder drainage in the female. *Am. J. Obstet. Gynecol.*, **96**, 773.
- Keltzer, W. A., Abreu, A., Navarro, I. *et al.* (1968). Urethral strictures: prevention with plastic indwelling catheters. *J. Urol.*, **99**, 187-188.
- Murray, K., Massey, A. and Feneley, R. C. L. (1984). Acute urinary retention—a urodynamic assessment. *Br. J. Urol.*, **56**, 468-473.
- Sethia, K. K., Selkon, J. B., Berry, A. R. *et al.* (1987). Prospective randomised controlled trial of urethral versus suprapubic catheterisation. *Br. J. Surg.*, **74**, 624-625.
- Shapiro, J., Hoffmann, J. and Jersky, J. (1982). A comparison of suprapubic and transurethral drainage for postoperative urinary retention in general surgical patients. *Acta Chir. Scand.*, **148**, 323-327.
- Taube, M. and Gajraj, H. (1989). Trial without catheter following acute retention of urine. *Br. J. Urol.*, **63**, 180-182.

The Authors

- A. F. Horgan, MB, Surgical Registrar.
- B. Prasad, FRCSI, Urology Registrar.
- D. Waldron, FRCSI, Senior Surgical Registrar.
- D. C. O'Sullivan, FRCS, FRCSI, Consultant Urologist.

Requests for reprints to: D. C. O'Sullivan, Department of Urology, Regional Hospital, Wilton, Cork, Ireland.

In vivo Detection by Microscopic Chromocystoscopy of Concurrent Urothelial Atypia in Superficial Bladder Cancer

A. IGUCHI, N. KINOSHITA and Z. MASAKI

Division of Urology, Department of Surgery, Saga Medical School, Saga, Japan

Summary—Microendoscopic observation of methylene blue-stained urothelial surfaces, so-called microscopic chromocystoscopy (MCC), was undertaken in 65 patients with superficial bladder cancer (Ta and T1) and its effectiveness in detecting concurrent urothelial dysplasia or carcinoma *in situ* was studied. A total of 166 biopsy samples were taken from 75 stained and 91 non-stained portions. Of 75 methylene blue-stained areas, 21 were judged to be abnormal (MCC-positive) by microscopic observation. Fourteen of these 21 MCC-positive areas (67%) were proven to be abnormal histologically, while 7 of 54 MCC-negative portions (13%) were histologically abnormal. Only 4 of 91 biopsies (4%) from non-stained mucosa were proven to have urothelial atypia. In per patient figures, 1 or more concurrent field changes were detected in 15 of 65 cases (23%). MCC contributed to the diagnosis in 10 of these 15 patients.

The concurrence of significant urothelial atypia with a primary vesical tumour is purported to be a possible sign of future tumour recurrence or of stage progression (Eisenberg and Schweinsberg, 1960; Schade and Swinney, 1973; Althausen *et al.*, 1976; Wolf and Hojgaard, 1983). It is difficult, however, to detect *in vivo* urothelial field change, such as dysplasia or carcinoma *in situ* of the bladder, by conventional cystoscopy. We previously suggested that microendoscopic observation of the methylene blue-stained bladder, so-called microscopic chromocystoscopy (MCC) is very useful for an *in vivo* diagnosis of tumour grade and for the detection of flat field change in either superficial or invasive bladder tumours (Iguchi, 1989).

In this report, the usefulness of MCC is studied, concentrating on its ability to detect field change in superficial bladder tumours.

Patients and Methods

A total of 96 patients with primary bladder cancer were treated in this institute between June 1984

and May 1989. Of these patients, 65 with histologically proven superficial transitional cell carcinoma (both Ta and T1) were included in this study.

Fifty ml of 0.1% methylene blue were instilled into the bladder for *in vivo* staining and retained intravesically for about 1 h. The methylene blue was then removed and after the bladder had been washed 3 times with 100 ml of normal saline each time, observations were made by a contact-microcystoscope. The Karl Storz contact-microcystoscope enables the observation of cytological details of the stained urothelium of the bladder (Gill *et al.*, 1983; Gill and Strauss, 1984). This instrument has dual optical systems which can be activated by pushing a knob from one position to another; one lens system has 1 to 60 times magnification and the other covers 20 to 150 times magnification. The microscope with the lower magnification can be used in essentially the same manner as a conventional cystoscope and the stained portions can be easily identified (Fig. 1). A close-up view using this instrument with 150 times magnification is shown in Figure 2. The change was defined as abnormal when large nuclei of varying sizes were observed, and/or when an irregular distribution was noted

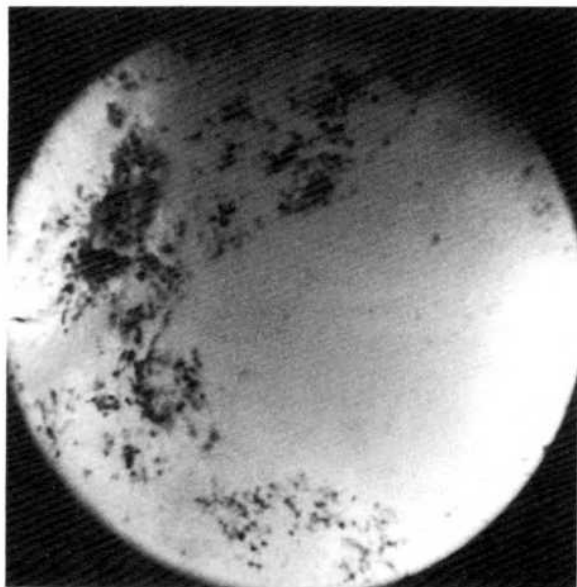


Fig. 1 Carcinoma *in situ* seen through the microscopical cystoscope with lower magnification after methylene blue staining.

(Fig. 2B, C). It was judged normal when small, round or spindle-shaped nuclei of a relatively uniform size were distributed regularly (Fig. 2A). An additional few minutes were usually required for this microcystoscopic observation compared with conventional cystoscopy. Immediately after micro-chromocystoscopic observation, cold cup biopsies were taken from the stained and non-stained mucosa of the bladder, this being followed by transurethral resection of the bladder tumour.

Staining of the non-tumorous flat mucosa is usually limited to a small area in a superficial bladder tumour. Essentially all of these stained portions were biopsied. The posterior side of the bladder neck and the retrotrigonal area were very often stained, probably due to trauma at the time of catheter insertion. Therefore, in the later half of the present series, biopsies of these portions were omitted when the portions were judged to be normal microendoscopically. Biopsies of the non-stained areas were taken from the parts just lateral to each ureteric orifice and retrotrigone, when tumours lesions or staining were absent in these areas.

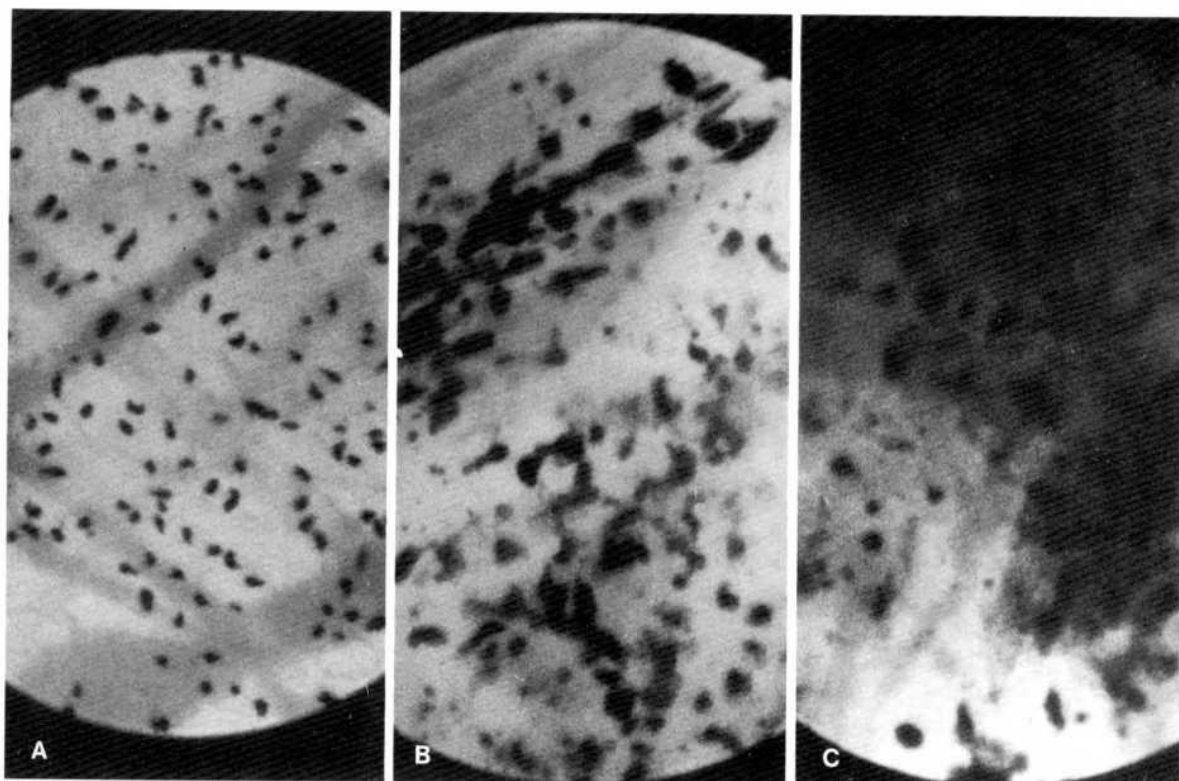


Fig. 2 *In vivo* urothelial surface observed through the microscopical cystoscope (150 $\times$ magnification). (A) Normal urothelium with small, round and regular nuclei (MCC findings: normal). (B, C) Abnormal urothelium showing deeply stained, irregular and crowded pleomorphic nuclei (MCC findings: abnormal).

Urothelial atypia of mucosal biopsy specimens was classified according to the UICC (1978) classifications.

Results

The series comprised 52 males and 13 females whose ages ranged from 49 to 89 years (average 69). Of these patients, 21 had grade 1 and 44 had grade 2 cancer. The pathological category was Ta in 53 patients and T1 in 12.

Intravesical instillation of methylene blue resulted in the selective staining of the main tumour of the bladder in 54 cases (83%). The mode of staining varied from spotty to diffuse and its intensity also varied. There was a tendency for tumours of a higher grade to be stained more deeply than lower grade tumours. Nine of 11 main tumours which were not stained were grade 1 lesions.

In all, 166 biopsy samples were taken from the non-tumorous urothelium in the 65 patients; 75 areas were stained and 91 were not stained (Table). Of the 75 stained mucosa, 21 (28%) showed significant nuclear abnormality, whereas 54 portions displayed a normal nuclear appearance (small, round and regular) in MCC observations. Histological study of 166 biopsied flat epithelia revealed urothelial dysplasia in 12 specimens and carcinoma *in situ* in 13; 8 were at the area adjacent to, and 17 were at the distant portion from, the main tumour. Twenty-one of 25 specimens with abnormal histology were taken from the stained epithelia. Only the remaining 4 were biopsied from the unstained parts. MCC-positive findings (21) predicted 14 field changes (dysplasia 5; carcinoma *in situ* 9), whereas only 7 of the 54 MCC-negative findings were histologically abnormal.

Irrespective of the number of abnormal biopsies, the data were analysed with reference to individual

patients. Significant field change was detected in 15 of the 65 patients (23%). In 12 of 15 patients, the abnormal biopsies were from the stained portions that could not be identified by conventional cystoscopy. In 10 of these 12 patients, MCC judgment of abnormality was consistent with the histological findings. In another 2 cases, however, abnormal histology was not consistent with the MCC findings, *i.e.* nuclear abnormality cannot be correctly predicted by microendoscopy. Only 3 patients were found to have field changes (dysplasia 2; carcinoma *in situ* 1) by random biopsies from non-stained areas.

Discussion

Many clinical studies have suggested that the presence of field change (dysplasia or carcinoma *in situ*) in the urothelium concurrent with a non-invasive papillary tumour is a significant risk factor indicating further recurrence or the future development of invasive cancer (Eisenberg and Schweinsberg, 1960; Schade and Swinney, 1973; Althausen *et al.*, 1976; Wolf and Hojgaard, 1983). It therefore appears important to detect these lesions prior to treatment.

Until now, detection of field change has been dependent upon random punch biopsy, and the detection rate has ranged from 33 to 52% (Heney *et al.*, 1978; Soloway *et al.*, 1978; Wallace *et al.*, 1979; Smith *et al.*, 1983; Harving *et al.*, 1988). In the present study, when we consider the results from random punch biopsies and disregard the staining character, field change was noted in 15 of 65 cases (23%), a rate which appears to be relatively low. However, it is recognised that the association rate of concurrent field change is greatly influenced by certain factors: how many patients with high grade tumours are included, whether or not the biopsy

Table Histology of 166 Mucosal Biopsies

Stained area		MCC findings	Histological findings of biopsied specimens					
			Dysplasia	CIS	Cystitis	Brunn's nests	Ca.	Normal
Stained	75	Abnormal	21	5	9	1	0	5
		Normal	54	4	3	0	2	44
Unstained	91		3	1	0	0	1	86
Total	166		12	13	1	2	3	135

CIS: carcinoma *in situ*.

Ca: papillary cancer.

was taken adjacent to the primary tumour, and how many random biopsies were taken. Since this study included only patients with superficial tumours and not those with grade 3 tumours, and since the number of biopsies taken per patient was 2.6, a 23% detection rate seems compatible with previously reported data. Almost the same values, 22% by Soloway *et al.* (1978) and 27% by Heney *et al.* (1978), were found when selection was limited to only grade 1 and grade 2 tumours. When compared with random punch biopsy, MCC appears extremely efficient at detecting field change associated with primary tumours.

In a previous study we found a tendency for the staining of low grade tumours and dysplasia to be weak compared with the clearer staining of high grade tumours (Iguchi, 1989). Therefore, there is the possibility that dysplastic change of flat epithelia could be overlooked if one depended solely on staining ability to portray field change. Nevertheless, the fact that the detection rate of field change by MCC was apparently high may indicate its efficiency in biopsies of flat epithelium. This should help to minimise the number of biopsies and thus reduce the risk of tumour implantation.

Because of false negative results (although the number is small), MCC should not replace random punch biopsy, but a combination of the 2 procedures does increase the detection rate of field change.

It has been reported that methylene blue staining alone can raise the detection rate of abnormal flat epithelium (Mufti *et al.*, 1990), although some regard it as inefficient (Vicente *et al.*, 1987). The main problem with this method when used without the microendoscope, however, is the high rate of false positive results. Microendoscopic observations reduce this rate. We have often observed linear staining at the posterior section of the bladder neck or spotty staining in the retrotrigonal area, but found that most of these areas displayed both normal nuclear appearance and normal configuration when observed microendoscopically and these findings accorded with the histological results. We therefore considered the findings to be due to instrumental injury of the mucosa. Other false-positive staining, such as inflammatory changes, can also be distinguished, to a certain extent, by microendoscopic observations.

It was therefore concluded that despite its limitations, MCC is a useful method for the *in vivo* detection of field change in superficial bladder tumours.

Acknowledgement

We thank Miss K. Miller for correcting the English in this report.

References

- Althausen, A. F., Prout, G. R. Jr. and Daly, J. J. (1976). Non-invasive papillary carcinoma of the bladder associated with carcinoma *in situ*. *J. Urol.*, **116**, 575–580.
- Eisenberg, R. B. and Schweinsberg, M. H. (1960). Bladder tumours and associated proliferative mucosal lesions. *J. Urol.*, **84**, 544–550.
- Gill, W. B., Huffman, J. L., Lyon, E. S. *et al.* (1983). *In vivo* urothelial surface histology by microscopic chromocystoscopy. *J. Urol.*, **130**, 669–671.
- Gill, W. B. and Strauss, F. H. (1984). *In vivo* mapping of bladder cancer (chromocystoscopy for *in vivo* detection of neoplastic urothelial surface). *Urology (Suppl.)*, **23**, 63–66.
- Harving, N., Wolf, H. and Melsen, F. (1988). Positive urinary cytology after tumor resection: an indicator for concomitant carcinoma *in situ*. *J. Urol.*, **140**, 495–497.
- Heney, N. M., Daly, J. and Prout, G. R., Jr. (1978). Biopsy of apparently normal urothelium in patients with bladder carcinoma. *J. Urol.*, **120**, 559–560.
- Iguchi, A. (1989). Clinical diagnosis of bladder cancer by microscopic chromocystoscopy. *Jpn. J. Urol.*, **79**, 1928–1936.
- Mufti, G. R., Shah, P. J. R., Parkinsson, M. C. *et al.* (1990). Diagnosis of clinically occult bladder cancer by *in vivo* staining with methylene blue. *Br. J. Urol.*, **65**, 173–175.
- Schade, R. O. K. and Swinney, J. (1973). The association of urothelial atypism with neoplasia: its importance in treatment and prognosis. *J. Urol.*, **109**, 619–622.
- Smith, G., Elton, R. A., Beynon, L. L. *et al.* (1983). Prognostic significance of biopsy results of normal-looking mucosa in cases of superficial bladder cancer. *Br. J. Urol.*, **55**, 665–669.
- Soloway, M. S., Murphy, W., Rao, M. K. *et al.* (1978). Serial multiple-site biopsies in patients with bladder cancer. *J. Urol.*, **120**, 57–59.
- UICC. Union Internationale Contre le Cancer (1978). *TNM Classification of Malignant Tumours*. Third edition. P. 113. Geneva: International Union against Cancer.
- Vicente, J., Chéchele, G. and Algaba, F. (1987). Value of *in vivo* mucosa-staining test with methylene blue in the diagnosis of pretumoural and tumoural lesions of the bladder. *Eur. Urol.*, **13**, 15–16.
- Wallace, D. M. A., Hindmarsh, J. R., Webb, J. N. *et al.* (1979). The role of multiple mucosal biopsies in the management of patients with bladder cancer. *Br. J. Urol.*, **51**, 535–540.
- Wolf, H. and Hojgaard, K. (1983). Prognostic factors in local surgical treatment of invasive bladder cancer with special reference to the presence of urothelial dysplasia. *Cancer*, **51**, 1710–1715.

The Authors

A. Iguchi, MD, Senior Lecturer.
N. Kinoshita, MD, Lecturer.
Z. Masaki, MD, Professor

Requests for reprints to: A. Iguchi, Division of Urology, Department of Surgery, Saga Medical School, Nabeshima 5-1-1, Saga 849, Japan.

Urological Audit: the Role for an Aggressive Approach to High Grade Superficial Bladder Tumours

S. R. MOHAMED, S. F. MISHRIKI, R. A. PERSAD, P. ABRAMS, J. C. GINGELL and R. C. L. FENELEY

Department of Urology, Southmead Hospital, Bristol

Summary—A retrospective study was undertaken of the different treatment modalities for bladder tumours under the care of 3 consultants in the urology department of a district general hospital. The aim was to review the results of the various forms of treatment. In all, 261 patients' case records were reviewed and 19 variables extracted.

There was an average delay of 4.2 months from the onset of symptoms to the initial cystoscopy. Over 50% of high grade tumours were invasive on initial presentation (G3T2/G3T3).

A range of treatments for the more aggressive tumours was adopted by the urologists, ranging from a conservative resection (TURBT) to an aggressive approach (cystourethrectomy) at the earliest sign of progression. A strong association between aggressive treatment and higher survival was noted.

This study has proved valuable in demonstrating to the urology team the value of routine audit and questioning "established" surgical practice. As a result, a more standard regime for the treatment of bladder tumours has been advocated and a prospective randomised controlled trial will be introduced.

The treatment of carcinoma of the bladder is controversial. In particular, the management of superficially invasive bladder cancer remains a challenge for the urologist. The results of a cautious approach using transurethral resection and radiotherapy for invasive carcinoma and high grade superficial carcinoma have been unsatisfactory (Wallace and Bloom, 1976; Herr, 1991). Birch and Harland (1989) reported some success with immunotherapy for recurrent multiple superficial carcinoma owing to the field change concept of multiple tumour origin. They advocated 2 courses of Bacillus Calmette-Guérin (BCG), reserving radical cystectomy if there was no response. There is a natural reluctance to adopt a more aggressive approach; prolonged surgery, the fear of high morbidity, abdominal stoma and impotence, result in a tendency to avoid performing cystectomies. The good response following continence and potency-

preserving cystoprostatectomy and substitution cystoplasty reported by Mundy *et al.* (1986) has further served to question the role of radiotherapy and the value of chemotherapy. Radical surgery in the management of high grade superficial cancer (G3T1) requires an early decision in order to prevent progression of tumour, especially when associated with carcinoma *in situ*. It was with a view to analyse the results of our management, find the outcome of different treatments for high risk and invasive bladder carcinomas, select the best agents, regimes and alternative treatments that this retrospective study was undertaken.

Patients and Methods

A retrospective study of patients with bladder cancer in the Bristol area from January 1985 to October 1990 was conducted. The study included 261 new cases of carcinoma of the bladder managed by different modes of treatment. The following

items were recorded after studying the case notes and histology reports: patient's age, sex, district of referral, symptoms and signs (microscopic haematuria, macroscopic haematuria, pain, dysuria and obstruction), interval between onset of symptoms and presentation to the general practitioner, interval between presentation to the hospital and time of first cystoscopy after investigations, relevant drug history, social history, findings on first cystoscopy and examination under anaesthesia (number, site, size of tumours and degree of fixation), treatment method, follow-up and progression. All histology results were retrieved from the histopathology reports. Information was databased (dbase III Plus) in order to allow sequential review and computer analysis of the data. There were 76 cases of high grade tumours (G3) and these were analysed for progression of disease.

Results

It was found that 75% of the patients were older than 65 years on presentation (Fig. 1). There was a delay in presentation of 2.7 months from the onset of symptoms and a further doctors' delay (period between the time first seen to the time management was instituted) of 1.5 months. More than 20% of the tumours were above 5 cm in size. Positive urine cytology was noted in 66% of high, 26% of moderate and 8% of low grade tumours (Fig. 2). The disease-free interval after first transurethral resection of grade 3 tumours at 6 months was 60% and at 2 years was 10% (Fig. 3). The grade 3 tumours were analysed with regard to their staging. The majority (51%) invaded muscle. The non-invasive superficial group included 22 patients with carcinoma *in situ* (Cis). There were 39 patients with invasive disease

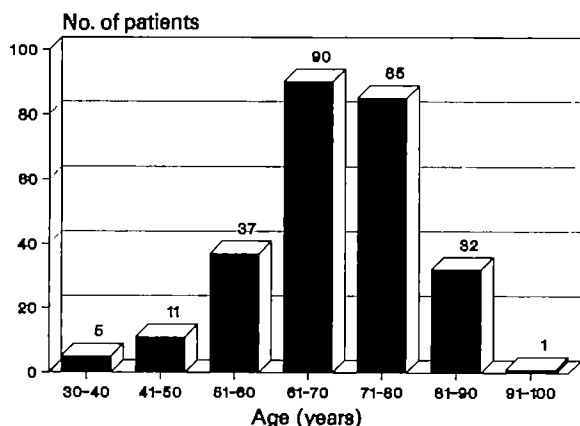


Fig. 1 Age of patients on initial treatment.

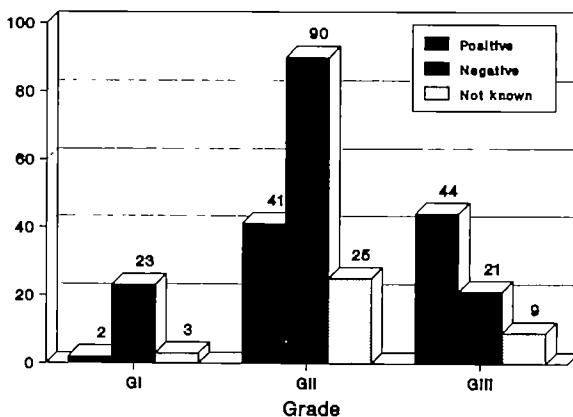


Fig. 2 Cytological findings and grades.

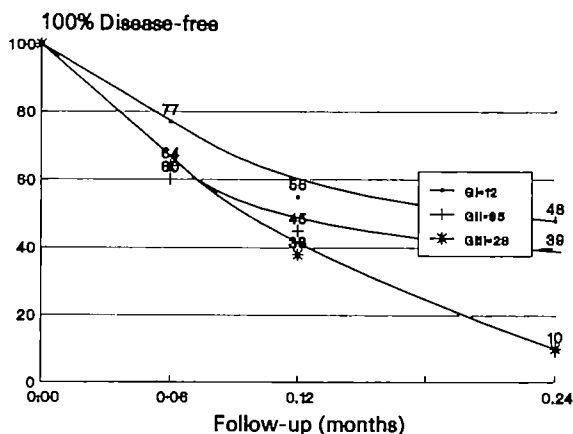


Fig. 3 Disease-free interval following cystoscopy and TURBT.

and 37 with superficial disease. Of the 39 patients in the invasive group, 18 had radiotherapy and 7 of them died within 2 years. There were 17 patients on follow-up with transurethral resection alone and 7 patients died over a follow-up period of 1 to 5 years. Four patients had a cystectomy; 1 died from post-operative peritonitis (Fig. 4).

The progression of tumour in the superficial group was then analysed. There were 25 patients whose tumour progressed; 22 patients had Cis associated with the tumour. Seven patients had G3 Cis alone which progressed and the other 15 patients had G3T1 with Cis. There were 6 patients with G3T1 without Cis whose tumour progressed, thus giving a total of 25 patients whose tumour progressed to muscle-invasive disease over a 2-year period. Five of these patients had radiotherapy and all died within 2 years. Seven patients who underwent cystectomy are alive and well. Of the 3 patients who had chemotherapy with Epydol, 1 died after completion of a single course.

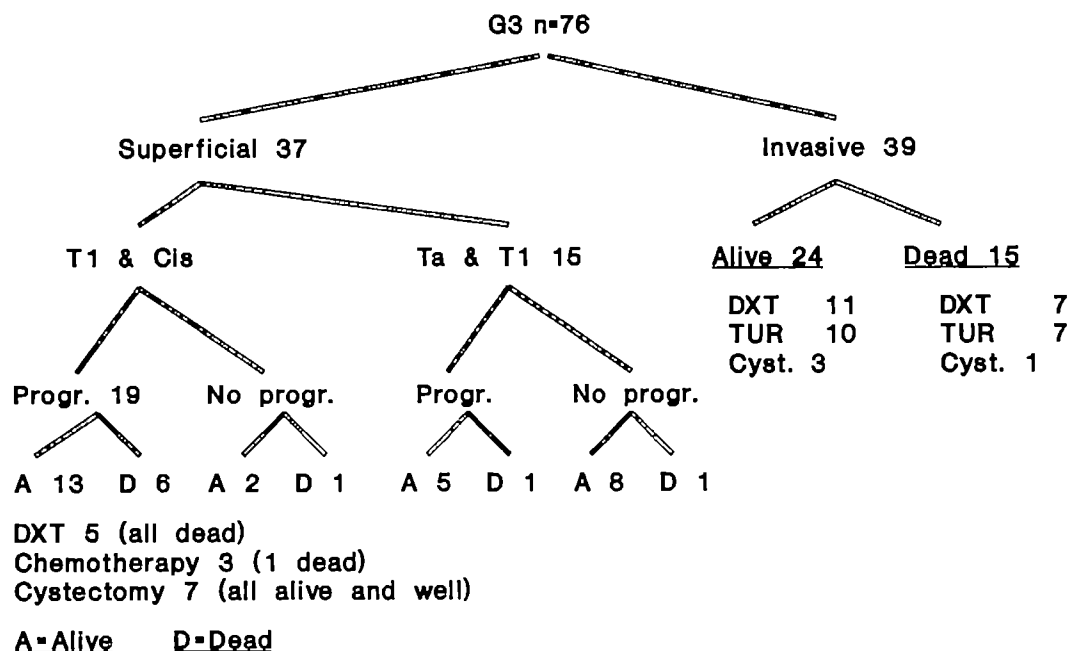


Fig. 4 Disease progression

Discussion

More than 50% of the high grade tumours were invasive at first cystoscopy. There was a total delay of 3 to 6 months before they were first cystoscoped. Wallace and Harris (1965) pointed out that most bladder tumours were probably curable when symptoms first appeared and that the survival rate of patients with infiltrating tumours fell from 65 to 25% when treatment was delayed for more than 1 month after the onset of bleeding.

Eighteen patients with invasive disease had radiotherapy, mostly palliative. Their results were poor. Five patients died within 2 years. Only 3 patients had cystectomy and the rest had transurethral resection. Skinner and Leiskovsky (1984) advocated radical cystectomy with *en bloc* pelvic iliac node dissection as being the best surgical therapy for high grade invasive carcinoma. Droller (1985) listed the problems of radiotherapy for invasive disease. Few patients respond without recurrence for a substantial length of time. For those who respond temporarily, post-radiation cystectomy may carry a higher morbidity and mortality.

Progression has been indicated by the development of muscle invasion or metastasis. Twenty-five patients had progression of the tumour. Althausen *et al.* (1976) recognised the difficulty in deciding the

correct management for G3T1 tumours. There was a 40% chance of developing invasive disease. With concurrent Cis there was an 80% chance of developing invasive disease within 18 months. The present study included 19 patients with Cis and this is consistent with other reports in the literature. In this study the average time to progression was 1.9 years.

Different modalities of treatment were adopted by different clinicians in the management of high grade superficial tumours. Cystectomy was performed only when other modalities failed and/or there was clear evidence of muscle invasion. The experience of Riddle *et al.* (1976) indicates that radiotherapy has little to offer in the management of widespread superficial Cis. It is ineffective in controlling superficial tumours and may make matters worse by inducing telangiectasia and encouraging bleeding (Bracken *et al.*, 1981).

Epodyl, the only drug used, produced dismal results. Fitzpatrick *et al.* (1979) also showed disappointing results with Epodyl. The anti-tumour activity of vaccine has been established as most dramatic on Cis, with a response rate of 75%. Sarosdy and Lamm (1989) found long-term benefits in 120 patients treated with Bacillus Calmette-Guérin who were followed up for 13 to 120 months; 78% had a good initial response. Ten patients required an intensive course of therapy with a final

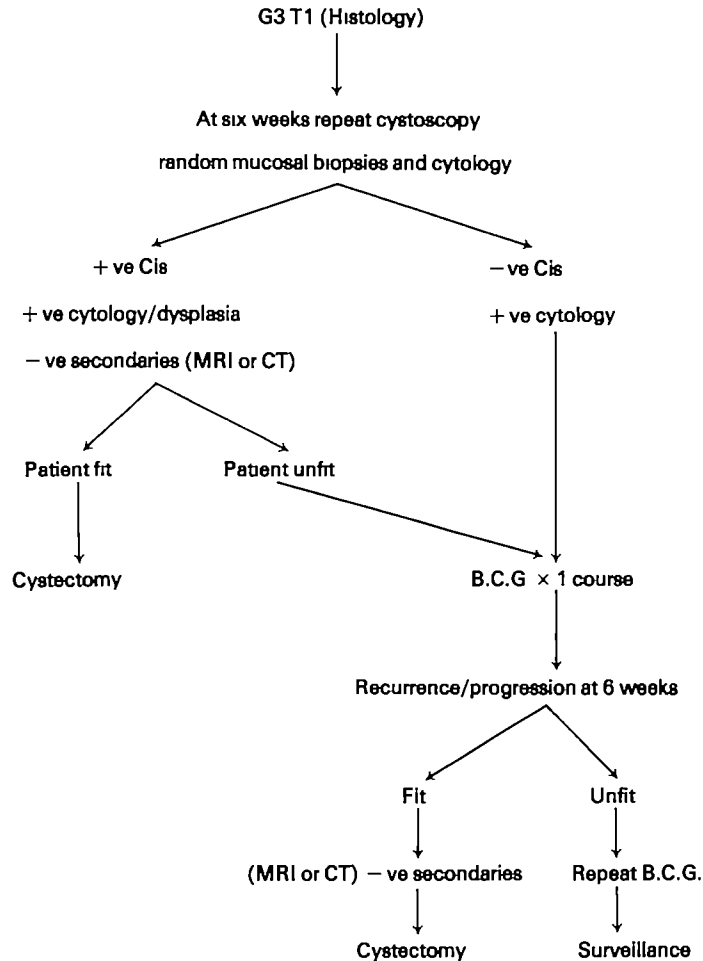


Fig. 5 Management flow chart

success rate of 89%. A reduction in the recurrence rate is useful in disease of low grade and stage. In high grade disease the aim is long-term prevention of progression to muscle-invasive disease. No controlled study has yet demonstrated that intravesical chemotherapy can achieve this (Heney *et al.*, 1982).

Soloway (1980) and Prout (1984) showed that one-third of patients with superficial tumours will not respond to chemotherapy. These were the poorly differentiated tumours with basement membrane breakthrough (T1 tumours). Herr (1991) emphasised that the T1 tumour category (lamina propria invasion) emerged as the only significant adverse prognostic variable before and after treatment. All 25 patients in this series were potentially curable at the time of presentation.

It is our opinion that patients should be considered for radical cystectomy when there is a threat of aggression of the primary tumour and the likelihood of spread into the deeper layers of the bladder. Once the high grade tumour has penetrated the lamina propria, radical cystoprostatectomy designed to preserve the innervation of the distal sphincter mechanism and the corpora cavernosa and substitution cystoplasty as described by Mundy *et al.* (1986) should be the preferred treatment. It is the usual practice to remove the urethra in patients with widespread field change. This operation (cystoprostatectomy) satisfies the field changes (Cis) which are common in this series.

Malkowicz *et al.* (1990) showed that cystectomy was highly effective in curing patients with high grade superficial disease, including those with

superficially invasive disease associated with nodal metastasis. If there is clear evidence of disease progression, especially if symptoms are severe, the bladder should be removed, since the disease is more extensive than apparent at cystoscopy. Magnetic resonance imaging (MRI) or CT scanning may help to define the depth of invasion, as there is a tendency to understage rather than overstage these tumours clinically (Nijhout *et al.*, 1985).

All 7 patients who underwent cystectomy for progression are alive and well. The results of early cystectomy are impressive. Stockle *et al.* (1987), in a series of 55 patients with G3 tumours alone, reported a 90% 5-year survival rate for patients with cystectomy for initial invasive T1 tumours, but for T1 patients with late cystectomies the 5-year survival rate was 61.5%.

Thus there is a need to identify patients at risk of progression and also to select the best agents, regimes and alternative strategies for the high grade superficial tumour with lamina propria invasion and associated Cis.

G3T1 tumours have been described as the "wolf in sheep's clothing". We would call it as the "silver lining amongst the clouds" and take the opportunity to offer the patient the option of cure with cystoprostatectomy, especially when associated with Cis. Our flow chart (Fig. 5) may be helpful, although a controlled clinical trial is necessary.

References

- Althausen, A. F., Prout, G. R., Jr and Daly, J. J. (1976). Non-invasive papillary carcinoma of the bladder associated with carcinoma *in situ*. *J. Urol.*, **116**, 575-580.
- Birch, B. R. P. and Harland, S. J. (1989). The pT1G3 bladder tumour. *Br. J. Urol.*, **64**, 109-116.
- Bracken, R. B., McDonald, W. M. and Johnson, D. E. (1981). Cystectomy for superficial bladder cancer. *Urology*, **18**, 459-463.
- Droller, M. J. (1985). The natural history of invasive bladder cancer and the case against definitive radiation therapy. *World J. Urol.*, **3**, 86-93.
- Fitzpatrick, J. M., Khan, O., Oliver, R. T. D. *et al.* (1979). Long-term follow-up in patients with superficial bladder tumours treated with intravesical Epodol. *Br. J. Urol.*, **51**, 545-548.
- Heney, N. M., Nocks, B. N., Daly, J. J. *et al.* (1982). Ta and T1 bladder cancer: location, recurrence and progression. *Br. J. Urol.*, **54**, 152-157.
- Herr, H. W. (1991). Progression of stage T1 bladder tumours after intravesical Bacillus Calmette-Guérin. *J. Urol.*, **145**, 40-44.
- Malkowicz, S. B., Nichols, P., Lieskovsky, G. *et al.* (1990). The role of radical cystectomy in the management of high grade superficial bladder cancer (PA, P1, PIS and P2). *J. Urol.*, **144**, 641-645.
- Mundy, A. R., Nurse, D. E., Dick, J. A. *et al.* (1986). Continence and potency preserving cystoprostatectomy and substitution cystoplasty for patients with bladder cancer. *Br. J. Urol.*, **58**, 664-668.
- Nijhout, M. A. E. M., Falke, T. H. M., Jones, B. *et al.* (1985). Magnetic resonance imaging of the bladder and prostate. *World J. Urol.*, **3**, 66-72.
- Prout, G. R. (1984). Superficial bladder cancer. In *Bladder Cancer*, ed. Smith, P. H. and Prout, G. R. Pp.151-171. London: Butterworth.
- Riddle, P. R., Chisholm, G. D., Trott, P. A. *et al.* (1976). Flat carcinoma *in situ* of bladder. *Br. J. Urol.*, **47**, 829-833.
- Saroady, M. F. and Lamm, D. L. (1989). Long-term results of intravesical Bacillus Calmette-Guérin therapy for superficial bladder cancer. *J. Urol.*, **142**, 719-722.
- Skinner, D. G. and Lieskovsky, G. (1984). Contemporary cystectomy with pelvic node dissection compared to pre-operative radiation therapy plus cystectomy in management of invasive bladder cancer. *J. Urol.*, **131**, 1069-1072.
- Soloway, M. S. (1980). The management of superficial bladder cancer. *Cancer*, **45**, 1856-1865.
- Stockle, M., Alken, P., Engelmann, U. *et al.* (1987). Radical cystectomy—often too late? *Eur. Urol.*, **13**, 361-367.
- Wallace, D. M. and Harris, D. L. (1965). Delay in treating bladder tumours. *Lancet*, **2**, 332-334.
- Wallace, D. M. and Bloom, H. J. G. (1976). The management of deeply infiltrating (T3) bladder carcinoma: controlled trial of radical radiotherapy versus pre-operative radiotherapy and radical cystectomy. *Br. J. Urol.*, **48**, 587-594.

The Authors

S. R. Mohamed, MS, Commonwealth Medical Fellow.
S. F. Mishriki, FRCS, Research Fellow.
R. A. Persad, FRCS, Registrar.
P. Abrams, FRCS, Consultant Urologist.
J. C. Gingell, FRCS, Consultant Urologist.
R. C. L. Feneley, ChM, FRCS, Consultant Urologist.

Requests for reprints to: S. F. Mishriki, Lithotripter Unit, Southmead Hospital, Westbury-on-Trym, Bristol BS10 5NB.

Initial Combination Chemotherapy with Cisplatin, Methotrexate and Vinblastine in Locally Advanced Transitional Cell Carcinoma—Response Rate and Pitfalls

S. D. FOSSÅ, S. J. HARLAND, S. B. KAYE, D. RAGHAVAN, J. M. RUSSELL, M. K. B. PARMAR, BARBARA M. USCINSKA, R. WOOD and the MRC Subgroup in Advanced Bladder Cancer (on behalf of the MRC Urological Working Party)

Department of Medical Oncology and Radiotherapy, Norwegian Radium Hospital, Oslo, Norway; Department of Oncology, Institute of Urology, London; CRC Department of Medical Oncology, Western Infirmary, Glasgow; Department of Clinical Oncology, Royal Prince Alfred Hospital, Sydney, Australia; MRC Cancer Trials Office, Cambridge

Summary—A total of 51 patients with locally advanced transitional cell carcinoma of the bladder were entered into a phase II study to evaluate the effect of initial cisplatin (100 mg/m², Day 2) combined with methotrexate (30 mg/m², Days 1 and 8) and vinblastine (4 mg/m², Days 1 and 8). Of 44 evaluable patients, 25 (57%) achieved an objective response of their primary bladder tumour (complete response (CR): 4 patients; partial response (PR): 21 patients); 30 of the 36 patients with micturition disturbances obtained relief. Toxicity was acceptable, but dose modifications due to haematological or renal toxicity were required in 153 of the 690 drug courses. Non-protocol dose modifications were performed 45 times.

The experience gained in this trial emphasises the need for improved co-operation between urologists, radiologists and clinical oncologists in such multicentre phase II studies. Difficulties were observed in adhering to dose modification rules, assessing pre-treatment tumour size (due to variation in quality of measure and in timing relative to initial transurethral resection (TUR)) and defining response to chemotherapy (due to failure to perform mandatory investigations at the right time). This study also illustrates that the accepted criteria for assessing response in the primary bladder tumour are difficult to apply in practice and that the results of any study using this indicator lesion require caution in their interpretation.

Objective responses (Miller *et al.*, 1981) have been observed in 40 to 70% of patients with advanced urothelial transitional cell carcinoma using combinations of the most active drugs: cisplatin (C), methotrexate (MTX), vinblastine (VB), doxorubicin (Harker *et al.*, 1985; Raghavan, 1988; Sternberg *et al.*, 1988; Hillcoat *et al.*, 1989; Tannock *et al.*, 1989; Logothetis *et al.*, 1990; Roberts *et al.*, 1991). Although most responses are partial, up to 30% complete response rates have been reported. Objec-

tive responses have been observed in distant metastases and in the primary tumour.

In 1987 the Medical Research Council (MRC) Advanced Bladder Cancer Subgroup of the Urological Cancer Working Party commenced a phase II study in T3/T4 MO transitional cell bladder carcinoma using a combination of cisplatin, methotrexate and vinblastine (CMV).

The object of this report was to present the response rate of CMV chemotherapy and review difficulties and sources of error in evaluating the response of the primary bladder tumour.

Patients and Methods

Eligibility criteria were as follows:

Histological proof of transitional cell carcinoma (TCC)

No previous systemic chemotherapy

T3 or T4NXMO category

Histological proof of deep muscle infiltration

No previous bladder surgery except for TUR

Performance status WHO 0, 1 or 2

Glomerular filtration rate >45 ml/min and serum creatinine <120 μ mol/l

White blood cell count $>3.5 \times 10^9$ /l and platelet count $>100 \times 10^9$ /l

No concomitant or previous malignancy other than basal cell carcinoma of the skin

Informed consent obtained.

Treatment. The following chemotherapy schedule (CMV) was used (Harker *et al.*, 1985):

Days 1 and 8: MTX 30 mg/m² + vinblastine 4 mg/m².

Day 2: Cisplatin 100 mg/m² if the glomerular filtration rate (GFR) was >60 ml/min.

Cisplatin 50 mg/m² if the GFR was 45 to 60 ml/min.

Days 2 and 9: Folinic acid 15 mg 24 and 30 h after MTX. (Harker *et al.* (1985) did not use folinic acid rescue).

Chemotherapy cycles were initiated at 3-weekly intervals. If a response was observed after 2 cycles, treatment was to be continued for a further 2 cycles.

Renal function was assessed by a measured creatinine clearance or by the Cockcroft formula (Cockcroft and Gault, 1976) and blood counts were monitored before each drug injection. Dose modifications were made on the basis of these results (Harker *et al.*, 1985). In particular, patients with GFR <45 ml/min were not to be given MTX or cisplatin. If the serum creatinine was >120 μ mol/l on Day 8 or had risen by at least 30% from Day 1 to Day 8, MTX was to be omitted. Full dose MTX and vinblastine was scheduled only if leucocytes were $>3.5 \times 10^9$ /l and platelets $>100 \times 10^9$ /l).

Response evaluation. According to the protocol, response was to be evaluated on the basis of assessment of the size of the primary tumour at the start of treatment, after 2 cycles and, where appropriate, after 4 cycles of chemotherapy. These assessments were to be made by cystoscopy, bimanual examination (giving 2 perpendicular tumour diameters) and by area measurements on

the computed tomography (CT) slice showing the greatest tumour extension.

The clinician recorded the response at 6 and 12 weeks to the Trials Office using the available measurements (clinician's assessment). Complete response (CR) corresponded to the disappearance of all clinical, radiological and histological evidence of the bladder tumour, and partial response (PR) corresponded to a 50% reduction in size of the primary tumour. If the CT gave an equivocal result, a PR was determined by bimanual examination alone.

At the final analysis we had to re-define the response criteria.

Revised assessment. A patient was evaluable if comparable measurements were recorded before and after 2 cycles of chemotherapy from at least 1 of the 3 types of examination—cystoscopy, bimanual examination or CT. A CR by these revised response criteria was defined as the disappearance of all malignant disease by all available measurements. If a biopsy was performed, this had to be negative for tumour (and for carcinoma *in situ*). A PR was equivalent to a reduction in tumour size of at least 50% by comparable measurements performed before and after treatment. An equivocal CT was interpreted as evidence of residual tumour. The "no change" (NC) and "progression" (PD) categories were defined in accordance with the WHO recommendations (Miller *et al.*, 1981).

Toxicity. Haematological and renal toxicity, nausea, vomiting and changes in performance status were systematically recorded.

Symptomatic response. Before each cycle of treatment the clinician evaluated the type and severity of micturition disturbances using an arbitrary scale (none, slight, moderate, severe). Complete symptomatic response was defined as relief of all urinary symptoms and pain. The complete disappearance of at least 1 symptom together with no deterioration in other urinary symptoms or pain was scored as partial symptomatic response.

Statistical methods. Approximately 45 evaluable patients were planned to be entered into this study. This would yield a standard error of approximately 6% in the final estimate of the response rate. Standard actuarial methods were used to analyse the survival data (Peto *et al.*, 1977). Data management was performed using COMPACT (Chilvers *et al.*, 1988).

Post-chemotherapy treatment. This was left to the decision of the individual clinician. A total of 31 patients received radiotherapy to the bladder, in some cases combined with TUR of the bladder tumour, and 7 patients underwent total cystectomy (in 4 cases performed as salvage cystectomy). One patient was given systemic chemotherapy with Mitomycin C. Two patients did not receive additional treatment. Information about post-chemotherapy treatment was lacking for 3 patients.

Results

Eight institutions entered 51 patients with muscle invasive bladder cancer (Table 1). Of these 51, 5 were deemed ineligible: 3 had a T2 tumour and 2 a renal function below that stated in the eligibility criteria (<60 ml/min). For 2 of the 46 eligible patients no treatment or response evaluation forms were available. These patients were not included in the response rate and toxicity analysis ("no data" in the tables).

Treatment. The 44 evaluable patients received 138 cycles of chemotherapy, with 2 patients receiving 1 cycle, 13 receiving 2 cycles, 6 receiving 3 cycles and 23 receiving the full 4 cycles; 33 patients started chemotherapy with full dose cisplatin (100 mg/m^2) in the first cycle of treatment and 11 started with reduced dose cisplatin (50 mg/m^2) owing to poor renal function ($\text{GFR} = 45\text{--}60 \text{ ml/min}$).

Response. Evaluation of objective response, based on CT and bimanual examination, was possible in

only 50% of the evaluable patients (Table 2). This was mainly due to a lack of appropriate measurements either before treatment or at 6 weeks. We thus re-defined the response criteria as presented in the "Patients and Methods" section. Table 3 shows the response observed using both the "clinician's assessment" and the "revised assessment". It can be seen that some of the clinician's assessments of response were downgraded in the revised assessment, but this downgrading was usually by 1 grade only (e.g. from CR to PR or PR to NC). In 1 patient with a relatively small tumour the clinician's assessment of response was changed from PR to progression using the revised criteria which included the CT result in this latter assessment. Overall, at 6 weeks, 30 of 44 patients (68%) achieved a response (CR or PR) using the clinician's assessment and 25 of 44 (57%) achieved a response using the revised assessment. Using the revised assessment, all of the complete responders sustained their response until 3 months and 2 of the partial responders at 6 weeks converted to complete response at 3 months.

Toxicity. Leucopenia was the most frequent haematological side effect but was usually grade 1 or 2 (Table 4). In 2 patients chemotherapy was discontinued after 1 cycle owing to renal toxicity. In a further 6 patients chemotherapy ceased after 3 cycles (in 5 because of general deterioration and in 1 for renal toxicity). Three cycles of therapy were delayed by up to 1 week because of haematological toxicity and/or elevated creatinine. A further 15 cycles were delayed for more than 1 week (range

Table 1 Characteristics of 46 Eligible Patients at Entry

			(%)
Age (years)	Median	65	
	Range	45–77	
Sex (n)	Male	35	(76)
	Female	11	(24)
Category (n)	T3	35	(76)
	T4a	4	(9)
	T4b	5	(11)
	Unknown	2	(4)
WHO performance status (n)	0	24	(52)
	1	19	(41)
	2	3	(7)
Serum creatinine ($\mu\text{mol/l}$)	Median	95	
	Range	60–123	
Haemoglobin (g/dl)	Median	13	
	Range	10.2–15.0	

Table 2 Measurement of Primary Tumour before Treatment and at 6 Weeks

	<i>No. of patients</i>	
	<i>Before treatment</i>	<i>At 6 weeks</i>
No measurement (neither bimanual nor CT)	5	5
CT only	15	11
Bimanual only	3	3
Both CT and bimanual	21	24
No data	2	2
Not applicable*	—	1
Total	46	46

* No assessment done, treatment discontinued after 1 cycle because of excessive toxicity.

17–42 days), with 10 of these delays occurring between the second and third cycles. The reason for delaying these 15 cycles has not been documented, but it seems likely that the timing of the cystoscopic assessment between the second and third cycles was responsible.

Other side effects which occurred frequently were gastrointestinal disturbances (nausea and vomiting) and oral mucositis (Table 5). Two patients experienced a white blood toxicity > grade 2 (Table 4). Skin problems, ototoxicity and neurotoxicity did not feature significantly in this study.

Figure 1 shows the renal toxicity. The average percentage change in creatinine values is shown separately for the 2 initial cisplatin doses (100 mg/m² and 50 mg/m²). As expected, the change in creatinine level was considerably greater in patients who received the full initial dose of 100 mg/m². With increasing numbers of cycles, elevations in serum creatinine by more than 30% were often observed, especially on day 8 of each cycle, with

recovery generally by the start of the subsequent cycle.

Dose modifications, either as omission or reduction of an individual drug, occurred in 150 of 690 scheduled single drug applications (Table 6). On 14 of these 150 occasions an inappropriate modification was made, while on a further 31 occasions doses should have been modified but were not.

Effect on post-chemotherapy treatment. Though not investigated systematically, the overall impression was that there was no increased toxicity in patients undergoing post-chemotherapy high dose radiotherapy or major surgery.

Symptomatic response. Of the 46 patients, 7 had no initial bladder symptoms, 1 was not assessed at 6 weeks and there were no data for 2. Of the remaining 36 patients, 23 (64%) exhibited complete relief of symptoms after 2 cycles of chemotherapy (Table 7). At 3 months, 20 of the 23 patients with initial bladder symptoms showed complete relief of symptoms. In most cases relief of micturition problems was recorded as early as after the first cycle.

Survival. The median follow-up was 25 months (range 3–33) (Fig. 2). The overall 1-year survival rate was 79% (95% confidence intervals (CI): 67–91%), the 18-month survival rate was 51% (95% CI: 36–66%) and the 2-year rate was 35% (95% CI: 19–50%).

Discussion

This phase II study confirms previous observations of a 50 to 60% objective response when locally advanced bladder cancer is treated with CMV

Table 3 Tumour Response Following a Minimum of 2 Cycles of Chemotherapy

<i>Response</i>	<i>At 6 weeks (n)</i>		<i>At 3 months (n)</i>	
	<i>Revised assessment</i>	<i>Clinician's assessment</i>	<i>Revised assessment</i>	<i>Clinician's assessment</i>
Complete	4	6	6	10
Partial	21	24	14	14
No change	12	12	1	1
Progression	4*	1	—	2
Not evaluable	2	0	3	1
No data	2	2	2	2
Not applicable	1†	0	20	16
Total	46	46	46	46

* One patient received only 1 cycle because of progression.

† Only 1 cycle because of renal toxicity.

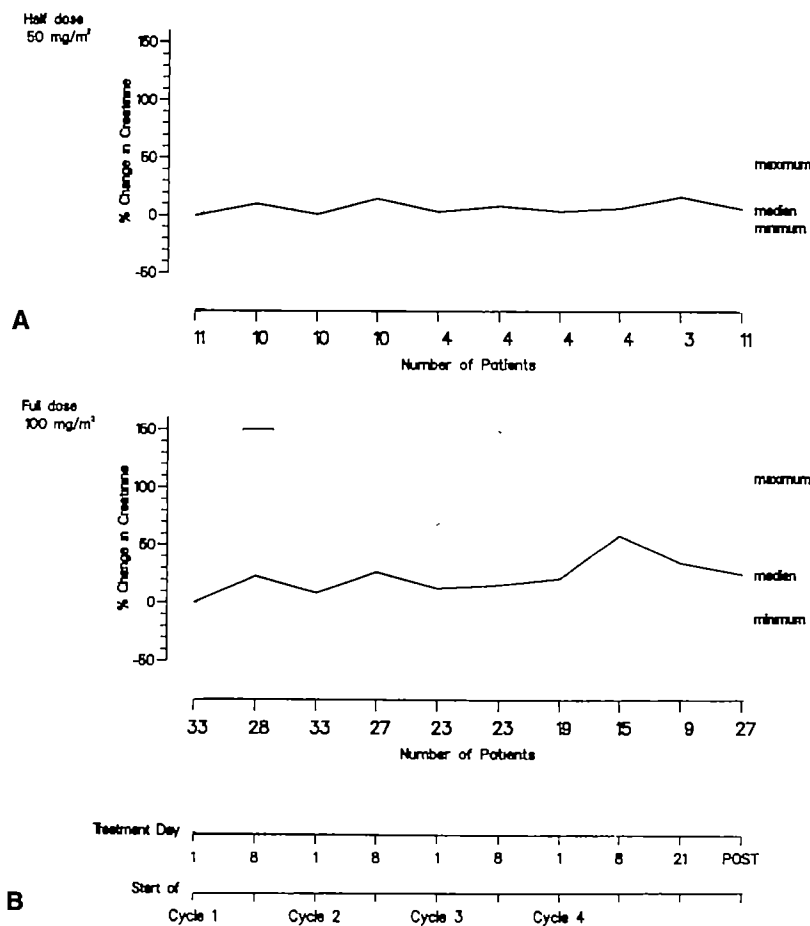


Fig. 1 Percentage change in serum creatinine during CMV treatment of bladder cancer patients. (A) initial half dose of cisplatin (50 mg/m²). (B) Initial full dose of cisplatin (100 mg/m²).

Table 4 Maximum White Blood Toxicity during Treatment

WHO toxicity grade	Treatment cycle				Overall
	1	2	3	4	
0	41	22	23	15	19
1	1	12	6	5	12
2	0	9	0	3	11
3	2	0	0	0	2
4	0	0	0	0	0
No data	2	2	2	2	2
Not applicable	0	1	15	21	0
Total	46	46	46	46	46

Data are numbers of patients.

chemotherapy (Harker *et al.*, 1985; Roberts *et al.*, 1991). It has been shown that although CMV chemotherapy is not a simple regimen to administer, objective and subjective toxicity was generally acceptable in this often elderly patient population. Careful supervision of patients is required since dose modifications, for example for transient elevations in serum creatinine, are not uncommon. There is evidence that this therapy eased micturition disturbances, a common and important problem for patients with advanced bladder cancer. This reinforces the finding of other groups of the beneficial symptomatic effects of cisplatin-based chemotherapy (Raghavan *et al.*, 1985; Fosså *et al.*, 1990). It is difficult to estimate, however, how much

Table 5 Maximum Toxicities over the Cycles Given

<i>Grade of toxicity</i>	<i>Nausea and vomiting</i>	<i>Oral</i>	<i>Skin</i>	<i>Ototoxicity</i>	<i>Neurotoxicity</i>
0	1 (2)	32 (73)	43 (97)	42 (98)	37 (86)
1	10 (23)	5 (11)	1 (2)	1 (2)	5 (11)
2	16 (36)	6 (14)	0	0	1 (2)
3	15 (34)	1 (2)	0	0	0
4	2 (5)	0	0	0	0
No data	2	2	2	2	3
Total	46	46	46	46	46

Data are number of patients (percentages in parentheses).

Table 6 Justified and Unjustified Dose Modifications

<i>Drug</i>	<i>Total no. of applications</i>	<i>Justified Omitted/reduced</i>	<i>Unjustified Omitted/reduced</i>	<i>Total no. of modifications</i>	<i>Failed Omitted/reduced</i>
MTX	276	56	6	62	19
VB	276	36	6	42	11
Cisplatin	138	44	2	46	1
Total	690	136	14	150	31

of this symptomatic relief resulted from chemotherapy rather than reduction of the tumour by TUR, the use of concomitant supportive therapy, or improved analgesic therapy.

This study has also highlighted the problems of conducting and interpreting the results of phase II

studies in patients with bladder cancer, particularly if the primary tumour is used as an indicator lesion. We shall review some of these problems here.

The chosen CMV schedule was expected to lead to a high degree of haematological and renal toxicity in patients with locally advanced bladder

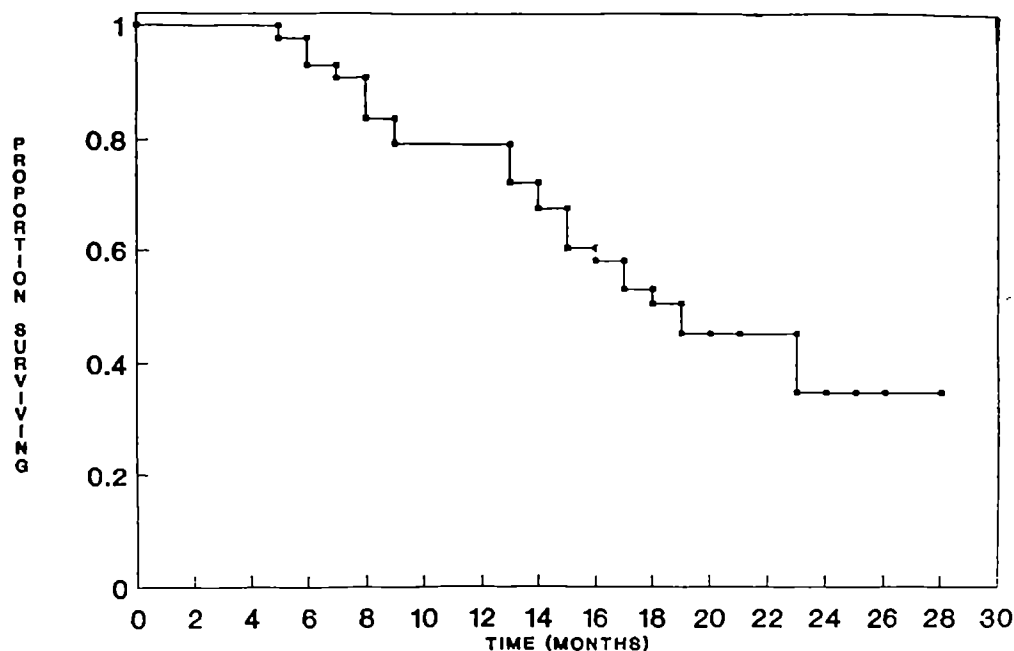
**Fig. 2** Overall survival in patients with T3/T4 bladder cancer receiving CMV chemotherapy as initial treatment.

Table 7 Relief of Bladder Symptoms

Relief	No. of patients (%)	
	At 6 weeks	At 3 months
Complete	23 (64)	20 (87)
Partial	7 (19)	0 (9)
No relief	5 (14)	2 (4)
Deterioration	1 (3)	1
Not applicable	8	21
No data	2	2
Total	46	46

cancer. The protocol therefore contained detailed guidelines for modifying doses of individual drugs. Our analysis has shown that the participating clinicians experienced difficulty in following these instructions. Inappropriate overdosage of MTX was the most frequent problem. In some cases this may have been because Day 8 injections were given not by the clinical oncologists but by a local urologist, physician or general practitioner who was less familiar with the dose modification guidelines set out in the protocol. This is certainly true for reasons of geography in many patients treated in Norway. A further cause of incorrect dose modifications may have been the practical difficulty experienced in obtaining a serum creatinine level before administering the drug.

Unfortunately, the protocol was ambiguous about whether pretreatment measurements were to be made before or after TUR, if one was performed. Thus it may be questioned whether in some instances observed responses were due to the chemotherapy, to a combination of surgery and chemotherapy, or even to surgery alone. From the data available it is difficult to judge to what degree this problem has influenced the results.

Response of the primary tumour was to be assessed by bimanual examination and by CT. When the data became available it was apparent that both methods were used at each assessment in only approximately 50% of the patients. One reason for this was that CT scans were not always possible at the time of evaluation because such resources are often scarce. Another reason was the lack of communication about protocol rules between the referring urologist and the oncologist before a patient was entered into the study. The urologist was often unaware that the patient might be suitable for the study and hence did not perform all of the investigations required by the protocol. Thus the definition of response had to be amended as outlined above.

When this protocol was activated we were aware of the potential for inaccuracies in the clinical examination of the primary bladder tumour. The hope was that CT would give more reliable measurements. The protocol described a detailed CT technique (thickness of slices, distance between slices) and recommended that area measurements be obtained directly from the most abnormal CT slice. However, even if the radiologist followed these recommendations, differences in examination methods might have been unavoidable. Variations in the type of CT machine, in the use of intravenous contrast during the CT examination and in the degree of fullness of the bladder have undoubtedly occurred. Furthermore, the protocol did not state any minimum time which had to elapse between a TUR and the CT examination. If CT of the bladder is done within a few days after TUR, a visible mass in the bladder wall due to tumour cannot easily be distinguished from that due to post-resection changes. Such variations may influence the final interpretation of the CT images of the bladder (Sager *et al.*, 1987a, b). No external review of the CT films has been performed.

At the time of writing the protocol it was not thought necessary to have biopsy proof of a complete response. At the present time it may be argued that such an investigation should have been mandatory. However, grave doubts have been raised about whether even this approach is as accurate and conclusive as is widely accepted. In fact, Scher *et al.* (1988, 1989) have shown that even when using clinical, bioptic and radiological methods to assess response, a correct result is obtained in only 70% of occasions when compared with a histopathological examination of the cystectomy specimen.

Given these considerations, we must interpret the results of this phase II study with some care. Most of the responses observed were partial and, in light of the discussion above, we cannot claim that the reported complete responses were true complete responses. Thus it is probably best to report an overall (clinical) response rate of 57%. However, it must be stated that even though this figure accords well with response rates reported in the literature, it may be prone to some error because of the problems discussed above.

The aim of any phase II study with its inherent biases—selection of patients and difficulties with assessment of response—is to consider whether the treatment under investigation shows sufficient promise to proceed to a proper test in a randomised trial against the standard therapy. A phase II trial

also offers a degree of training to individuals in learning to use and become familiar with the new treatment. In these respects this study has proved to be very fruitful, despite its obvious shortcomings. It has highlighted the fact that employing multimodal therapy (chemotherapy plus cystectomy/radiotherapy) requires good collaboration between the oncologist, urologist, radiotherapist and diagnostic radiologist. In addition, the results of this study, together with the experience from the medical literature (Harker *et al.*, 1985), led the MRC Subgroup in Advanced Bladder Cancer to initiate an international randomised trial of neoadjuvant CMV chemotherapy in locally advanced bladder cancer. The trial, in which the principal endpoint is survival, aims to recruit 1,000 patients to assess reliably the role of neoadjuvant chemotherapy in locally advanced bladder cancer.

Acknowledgements

The authors thank Dr J. J. Bolger, Weston Park, Sheffield, and Dr S. M. Crawford, Clinical Oncology Unit, University of Bradford, and Drs A. G. Robertson, R. P. Rampling and N. S. Reed, Western Infirmary, Glasgow, for their participation in this study

References

- Chilvers, C. E. D., Fayers, P. M., Freedman, L. S. *et al.* (1988). Improving the quality of data in randomised clinical trials: the COMPACT computer package. *Stat. Med.*, **7**, 1165–1170
- Cockcroft, D. W. and Gault, M. H. (1976). Prediction of creatinine clearance from serum creatinine. *Nephron*, **16**, 31–41
- EORTC-GU Group, Denis, L., Bukowski, R. *et al.* (1990). The prognostic value of the pT-category after combination chemotherapy for patients with invasive bladder cancer who underwent cystectomy. In *Neoadjuvant Chemotherapy in Invasive Bladder Cancer*, ed. Splinter, T. A. W. and Scher, H. I. Pp. 219–224. New York: Wiley-Liss.
- Fossá, S. D., Sager, E. M., Hosbach, G. *et al.* (1990). Cisplatin and medium dose Methotrexate in advanced transitional cell carcinoma of the urinary tract. *Scand. J. Urol. Nephrol.*, **24**, 199–204
- Harker, G. W., Meyers, F. J., Freiha, F. S. *et al.* (1985). Cisplatin, Methotrexate and Vinblastine (CMV): An effective chemotherapy regimen for metastatic transitional cell carcinoma of the urinary tract. A Northern California Oncology Group Study. *J. Clin. Oncol.*, **3**, 1463–1470
- Hillcoat, B. L., Raghavan, D., Matthews, J. *et al.* (1989). A randomized trial of cisplatin versus cisplatin plus methotrexate in advanced cancer of the urothelial tract. *J. Clin. Oncol.*, **7**, 706–709
- Logothetis, C. J., Dexous, F. H., Finn, L. *et al.* (1990). A prospective randomized trial comparing MVAC and CISCA chemotherapy for patients with metastatic urothelial tumours. *J. Clin. Oncol.*, **8**, 1050–1055
- Miller, A. B., Hogstraten, B., Stagnut, M. *et al.* (1981). Reporting results of cancer treatment. *Cancer*, **47**, 207–214
- Peto, R., Pike, M. C., Armitage, R. *et al.* (1977). Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. *Br. J. Cancer*, **35**, 1–39
- Raghavan, D. (1988). Pre-emptive intravenous chemotherapy for invasive bladder cancer. *Br. J. Urol.*, **61**, 1–8
- Raghavan, D., Pearson, B., Duval, P. *et al.* (1985). First-line intravenous cis-platinum: improved management for invasive high-risk bladder cancer. *J. Urol.*, **133**, 399–402
- Roberts, J. T., Fossá, S. D., Richards, B. *et al.* (1991). Results of Medical Research Council phase II study of low dose cisplatin and methotrexate in the primary treatment of locally advanced (T3 and T4) transitional cell carcinoma of the bladder. *Br. J. Urol.*, **68**, 162–168
- Sager, E. M., Fossá, S. D., Kaalhus, O. *et al.* (1987). Contrast-enhanced CT in carcinoma of the urinary bladder. The use of different injection methods. *Acta Radiol. (Diagn.)*, **28**, 67–70
- Sager, E. M., Talle, K., Fossá, S. D. *et al.* (1987). Contrast-enhanced CT to show perivesical extension in muscle invasive bladder cancer. *Acta Radiol.*, **28**, 307–311
- Scher, H., Herr, H., Sternberg, C. *et al.* (1989). Neo-adjuvant chemotherapy for invasive bladder cancer. Experience with the M-VAC regimen. *Br. J. Urol.*, **64**, 250–256
- Scher, H. I., Yagoda, A., Herr, H. W. *et al.* (1988). Neoadjuvant M-VAC (Methotrexate, Vinblastine, Doxorubicin and Cisplatin) effect on the primary bladder lesion. *J. Urol.*, **139**, 470–474
- Sternberg, C. N., Yagoda, A., Scher, H. I. *et al.* (1988). M-VAC (Methotrexate, Vinblastine, Doxorubicin and Cisplatin) for advanced transitional cell carcinoma of the urothelium. *J. Urol.*, **139**, 461–469
- Sternberg, C. N., Yagoda, A., Scher, H. I. *et al.* (1989). Patterns of response, survival and relapse in advanced urothelial cancer following M-VAC therapy. *Proc. ASCO*, **8**, 129
- Tannock, I., Gospodarowicz, M., Connolly, J. *et al.* (1989). M-VAC (Methotrexate, Vinblastine, Doxorubicin and Cisplatin) chemotherapy for transitional cell carcinoma: The Princess Margaret Hospital experience. *J. Urol.*, **142**, 289–292

The Authors

- Sophie D. Fossá, MD, PhD, Consultant, Department of Medical Oncology and Radiotherapy, Norwegian Radium Hospital, Oslo
- S. J. Harland, MD, MSc, MRCP, Senior Lecturer, Department of Oncology, Institute of Urology, London
- S. B. Eaye, MD, Professor, CRC Department of Medical Oncology, Western Infirmary, Glasgow
- D. Raghavan, PhD, FRACP, Research Director, Urological Cancer Research Unit, Department of Clinical Oncology, Royal Prince Alfred Hospital, Sydney, Australia
- J. M. Russell, FRCP, Consultant Radiotherapist, Western Infirmary, Glasgow
- M. K. E. Parmar, PhD, Statistician, MRC Cancer Trials Office, Cambridge
- Barbara M. Uscinska, Data Manager, MRC Cancer Trials Office, Cambridge
- R. Wood, BSc, MSc, Computer Programmer, MRC Cancer Trials Office, Cambridge

Requests for reprints to: Sophie D. Fossá, MRC Cancer Trials Office, 1 Brooklands Avenue, Cambridge, CB2 2BB, UK.

Intravesical Instillation of Beta-Interferon in the Treatment of Bladder Cancer

R. MIGLIARI*, M. EL DEMIRY, G. MUSCASCAS and E. USAI

Department of Urology, University of Cagliari, Italy; * Police Hospital, Cairo, Egypt

Summary—A total of 36 patients with single superficial bladder cancer TNM stage Ta–T1/G2 was studied over a 24-month period before entering the study to evaluate the efficacy and tolerance of high doses of beta-interferon (beta-INF); 24 patients had a primary tumour (group 1) and 12 had had more than 3 recurrences (group 2). They received 8 intravesical doses of beta-INF, 50,000,000 IU in 50 ml sterile water, at weekly intervals, 15 days after transurethral resection of the bladder (TURB).

Efficacy was estimated by simple recurrence rate and by the person-years method. The recurrence rate was 25% in group 1 with a mean follow-up of 21.6 months. Comparison with the recurrence rate of a historical control group treated only by TUR showed that there was a slight statistically significant difference. Group 2 had a recurrence rate of 100% in the period before beta-INF (follow-up 24 months) and 91% after INF administration (mean follow-up 20.5 months).

Patients were questioned about side effects before and after each treatment; tolerance of the drug was excellent. The results suggest that beta-interferon could be safely used as a prophylactic agent against the recurrence of primary superficial bladder cancer. Its efficacy seems comparable to that obtained with other current chemoprophylactic agents.

High recurrence rates following local resection of superficial bladder tumours indicate that transurethral resection cannot be considered to be the definitive therapy in most cases (Soloway and Martino, 1976; Loening *et al.*, 1980). Therefore, topical chemoprophylaxis has become an essential part of the treatment of these malignancies. Several major advances have been made in the treatment of recurrences, but none of the drugs tested can be considered ideal.

Various clinical studies have been conducted to evaluate the efficacy of different types of interferon (IFN) preparations in recurrent papillary tumours of the urinary bladder and carcinoma *in situ* (Ikic *et al.*, 1981; Scorticatti *et al.*, 1982; Torti *et al.*, 1984; Oliver *et al.*, 1986). These reports have considered both the direct anti-proliferative activity of the molecules and their modulatory effects on immunity (Borden *et al.*, 1984; Shapiro *et al.*, 1984; Grups *et al.*, 1985).

At present, the usefulness of interferon in the treatment of superficial bladder cancer is not clearly defined. In fact, there is no agreement among investigators about the most effective treatment regimen, in particular the duration and frequency of treatment, the activity of various types of INF and the most appropriate doses.

We report our experience of 36 patients with superficial bladder cancer who received intravesical instillation of high doses of beta-interferon (50,000,000 IU). We evaluated the tolerance and effectiveness of this agent in recurrences of superficial bladder cancer after transurethral resection of the neoplasm.

Patients and Methods

A total of 36 patients (28 males and females) with superficial transitional cell carcinoma (TCC) was treated with beta-interferon at the Urologic Clinic of Cagliari from January 1986 onwards. The mean age was 61 years (range 42–69). All patients had

a single papillary tumour treated by deep transurethral resection. Measured by ultrasound, the tumours ranged in size from 1.3 to 3.4 cm, with an average size of 2.2 cm. Histologically, all tumours were Ta-T1 G2. Twenty-four patients (Group 1) had a primary tumour. Twelve of 36 patients (Group 2) had a previous history of resection of superficial bladder cancer (Ta-T1 G2) treated with various drug regimes (bleomycin, mitomycin C or epirubicin).

None of the Group 1 patients had received prior chemotherapy or radiotherapy for other neoplasms.

Pre-treatment investigations included a complete medical history and clinical examination, including height and weight, complete blood count with differential and platelet count, liver and renal function tests. Chest X-ray and ECG were performed on each patient. All subjects were required to have 80–100% performance status (Karnofsky index), normal haematological, renal and hepatic functional measurements; in particular, eligibility for entry required peripheral WBC over 3500 (with normal differential count and platelet count $\geq 100,000$ as well as serum creatinine $< 250 \mu\text{mol/L}$ and serum bilirubin $> 25 \mu\text{mol/L}$). Written informed consent was required prior to entering the study.

Treatment started 15 days after TUR of the visible lesion, if, at a second examination, a check cystoscopy was negative and cytology confirmed that the transurethral resection was radical.

The treatment protocol consisted of 50,000,000 IU beta-interferon (Frone, Ares-Serono Group, Milan, Italy) in 50 ml of saline by instillation weekly for 8 weeks. Patients were instructed to retain the drug for 2 h if possible. Other therapies were not allowed during INF treatment.

Every 3 months patients underwent urine analysis followed by cystoscopy, cytological examination of bladder washings and biopsy of any suspicious area. In addition, a bone scan, chest X-ray and liver sonography were performed every 6 months. A new visible tumour or a positive cytology result was considered to be a recurrence. Treatment was stopped if recurrence or progression was evident at any time. Toxicity was recorded from the start of therapy according to the WHO (1979) criteria. Complete response was recorded if no evidence of disease was detected following cytological investigation and endoscopy at 24 months.

Results were estimated by simple recurrence rate and by the modified person-years method (Schoenberg and Myers, 1977) during the 2 years following beta-IFN therapy.

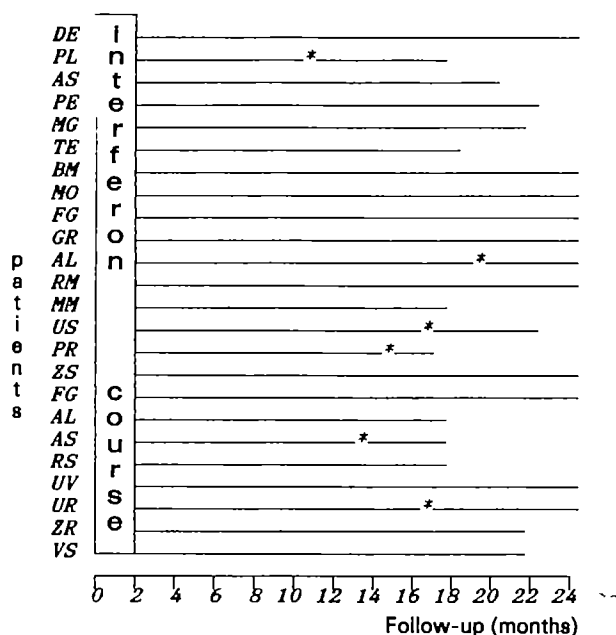


Fig. 1 Clinical history of patients with primary TCC (Group 1) after INF therapy.

Statistical analysis was carried out according to Student's *t* test and the person-years method.

Results

Thirty-six patients have entered this study to date. Of these, 28 were male (mean age 59.5 years) and 8 were female (mean age 57.7 years). All received 6 courses of beta-interferon. Figure 1 represents the clinical course of patients with bladder tumour (primary TCC) for 24 months after INF therapy (Group 1). Figure 2 shows the clinical history of patients with recurrent bladder tumours 24 months before and after IFN therapy (Group 2).

Group 1 included patients who presented with bladder tumours and who received transurethral resection followed by INF therapy. After treatment there were 6 instances (24 patients) of tumour recurrence in 519 patient-months.

The recurrence rate was compared with that of a previous control group treated only with TUR (Table 1). The simple recurrence rate was 25% in INF patients and 38.5% in the previous control group. According to the person-years method the number of recurrent tumours per patient-months was 0.011 in INF-treated patients and 0.038 in previous groups ($P < 0.05$). In Group 2 (patients with recurrent tumour) there were 42 episodes of

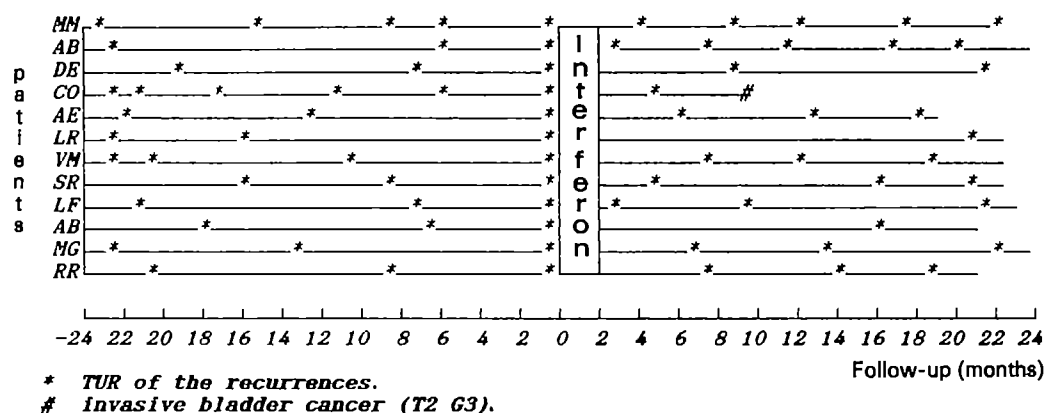


Fig. 2 Clinical history of patients with TCC (Group 2) before and after INF therapy.

tumour recurrence in 288 patient-months during the 24 months before INF, and 34 episodes (12 patients) of recurrence in 247 patient-months after treatment.

The simple recurrence rate was 91% after therapy. According to the person-years method the number of recurrent tumours per patient-months was 0.137 before and 0.145 after INF therapy. This did not demonstrate a statistically significant decrease in recurrent tumour following INF therapy (Table 2).

None of the patients experienced acute adverse side effects. Two patients presented with frequency of micturition and dysuria due to a urinary tract infection which improved after appropriate antimicrobial therapy. No changes in either the voided volume or the frequency of micturition were observed during the 6 weeks of therapy, apart from the transient episodes mentioned above. In particular, no abnormalities such as leukopenia, throm-

bocytopenia or elevation of GOT and GPT were demonstrated. After 3 months 1 patient had progression of disease, presenting a T1G3N1M1 bladder neoplasm. He died after 2 months.

Apart from this patient, histological examination of the biopsies of suspicious areas revealed a TaG2 transitional cell carcinoma recurrence in 2 group 2 patients; in the other suspicious areas moderate or mild dysplasia and chronic cystitis were found; those field changes were not regarded as strictly related to beta-interferon treatment.

Discussion

Considerable interest has been focused on the use of interferon and INF-inducers as anti-neoplastic agents in man. A review of the literature, much of which is preliminary, suggests that interferon therapy for TCC may modify the biological behaviour of this disease and provide clinical benefit for some patients.

Table 1 Summary of Recurrence Rate in 24 Patients in the 24 Months after INF Therapy and Comparison with Historical Controls

	INF patients	Historical controls
Simple recurrence rate		
No. of patients	24	70
No. of patients with recurrences	6	27
Recurrence rate (%)	25*	38.5
Person-year method		
Total no. of recurrences	6	43
Total no. of patient-months	519	1202
No. of recurrences/patient-months	0.011†	0.036

* $P < 0.05$.

† $P < 0.05$.

Table 2 Summary of Recurrence Rate in 12 Patients in the 24 Months before and after INF Therapy

	Before INF	After INF
Simple recurrence rate		
No. of patients	12	12
No. of patients with recurrences	12	10
Recurrence rate (%)	100*	91
Person-years method		
Total no. of recurrences	42	34
Total no. of patient-months	288	271
No. of recurrences/patient-months	0.145†	0.125

* $P = n.s.$

† $P = n.s.$

Hara *et al.* (1990) compared the efficacy of various interferons in a bladder cancer cell line and showed that beta-interferon was more effective than alpha- or gamma- interferon in inhibiting cell proliferation, and that the response was dose-dependent. Anti-mitotic effects may underlie, at least in part, the potential therapeutic activity of INF for bladder carcinoma (Borden *et al.*, 1984) but interferon may also play a pivotal role in the immune response, enhancing natural killer cell activity and influencing macrophage activity (Droller and Gromolka, 1984).

We report the clinical results of our initial experience with the use of intravesical beta-interferon in the prophylaxis of primary tumours (group 1) and highly recurrent superficial bladder tumours (group 2).

In patients with a high recurrence rate, treatment with interferon did not seem to interfere significantly with the natural history of the tumour and no significant modifications were observed with respect to the duration of disease-free periods. Also, there was no significant difference in the recurrence rates before and after INF treatment. According to the person-years method, the number of recurrences per patient—months decreased only slightly after INF and was not statistically significant.

These data appear to confirm similar results reported by Grups *et al.* (1985, 1987) with alpha-2 interferon.

It is necessary to stress that all of these patients failed to respond to other cytotoxic drugs (bleomycin, mitomycin C or epirubicin) and that all had received at least 2 different drugs in different courses before INF therapy. This lack of response to conventional drugs seems to suggest either the persistence of an unknown tendency to develop tumours or some resistance of the urothelial mucosa to chemotherapy.

Results obtained in group 1 patients are interesting. A slight statistically significant difference in terms of recurrence rate was found between patients who received INF and the control group treated only by transurethral resection. According to the person-years method the probability of recurrences in the first group (INF after TUR) was statistically significantly decreased ($P > 0.05$). In fact, the number of recurrences per patient-months was 0.011 in INF-treated patients and 0.038 in patients treated with TUR alone.

With respect to drug tolerance, it is important to note that other drugs currently employed can cause substantial toxicity, such as myelosuppression (thiotepa) (Veenema *et al.*, 1962), chemical cystitis

and contact dermatitis (mitomycin C, doxorubicin and ethoglucid) (Devonoc *et al.*, 1983; Garnick *et al.*, 1985) and bladder irritability (BCG) (Martinez-Pineiro *et al.*, 1990).

The main advantage demonstrated by this and other trials with interferons is the minimal toxicity observed even with high dosage regimens.

In conclusion, our results suggest that the intravesical administration of beta-interferon could play a role in the management of superficial bladder cancer. However, cost must also be considered when deciding whether to use interferons or other agents; further double-blind, randomised, multicentre studies are required to define more clearly the role and future of this drug in the treatment of superficial bladder cancer.

References

- Borden, E. C., Groveman, D. S., Nasa, T. *et al.* (1984). Antiproliferative activities of interferons against human bladder carcinoma cell lines *in vitro*. *J. Urol.*, **132**, 800–803.
- Devonoc, M., Bouvier, R., Sarkissian, J. *et al.* (1983) Intravesical instillation of mitomycin C in the prophylactic treatment of recurring superficial transitional cell carcinoma of the bladder. *Br. J. Urol.*, **55**, 676–679.
- Droller, M. J. and Gomolka, D. (1984). Macrophage depletion and manipulation of enhanced immune response in an animal model of bladder cancer. *Cell. Immunol.*, **83**, 433–441.
- Garnick, M. B., Schade, D., Israel, M. *et al.* (1985). Intravesical doxorubicin for prophylaxis in the management of recurrent superficial bladder carcinoma. *J. Urol.*, **131**, 43–47.
- Grups, J. W., Frohmüller, H. G. and Ackermann, R. (1985). Immunological findings in patients with superficial bladder cancer during human alpha-2-interferon treatment. *Urol. Int.*, **40**, 6, 301–306.
- Grups, J. W., Frohmüller, H. G. and Ackermann, R. (1987). Can recombinant human alpha-2 interferon prevent recurrence of high grade superficial bladder tumors? *Cancer Detect. Prev.*, **10**, 5–6, 405–409.
- Hara, M., Yoshimoto, J., Matsumura, Y. *et al.* (1990). Intravesical instillation therapy using interferon for treatment of bladder cancer. In *Immunotherapy of Urological Tumors*, ed. De Kernion, J. B. Pp. 129–137. London, Edinburgh: Churchill Livingstone.
- Ikic, D., Maricic, Z., Oresic, V. *et al.* (1981). Application of human leucocyte interferon in patients with urinary bladder papillomatosis, breast cancer, and melanoma. *Lancet*, **1**, 1022.
- Loening, S., Narayana, A. and Yoder, L. (1980) Factors influencing the recurrence rate of bladder cancer. *J. Urol.*, **31**, 123–129.
- Martinez-Pineiro, J. A., Jimenez Leon, J., Martinez-Pineiro, L., Jr. *et al.* (1990). BCG vs doxorubicin vs Thiotepa instillation for primary superficial bladder cancer. Interim report of a randomized prospective study. In *Immunotherapy of Urological Tumors*, ed. De Kernion, J. B. Chapter 8, pp. 59–68. London, Edinburgh. Churchill Livingstone.
- Oliver, R. T. D., Waxman, J. H., Kwok, H. *et al.* (1986). Alpha lymphoblastoid interferon for non-invasive bladder cancer. *Br. J. Cancer*, **53**, 432–433.
- Schoenberg, B. S. and Myers, M. H. (1977). Statistical method

- for studying multiple primary malignant neoplasms. *Cancer*, **40**, 1892-1898
- Scorticatti, C. H., de La Pena, N. C., Bellora, O. G. *et al.* (1982). Systemic IFN-alpha treatment of multiple papilloma grade I or II patients. pilot study. *J. Interferon Res.* **2**, 339-343.
- Shapiro, A., Ratliff, T. L., Kelley, D. R. *et al.* (1984) Heightened interferon-gamma production by mononuclear cells from bladder cancer patients. *Cancer Res.*, **44**, 3140-3143.
- Soloway, M. S. and Martino, C. (1976). Prophylaxis of bladder tumor implantation. *Urology*, **7**, 29-33.
- Torti, F. M., Shortliffe, L. D. and Williams, R. D. (1984). Superficial bladder cancers are responsive to alpha-2 interferon administered intravesically *Proc Am Soc. Clin Oncol.*, **3**, 160
- Veenema, R. J., Dean, A. L., Jr., Roberts, M. *et al.* (1962) Bladder carcinoma treatment by direct instillations of thiotepa. *J. Urol.*, **88**, 60-63
- WHO (1979). *Handbook for Reporting Results of Cancer Treatment* WHO Offset Publication No. 48. Geneva: WHO.

The Authors

- R. Migliari, MD, Senior Registrar, Department of Urology, Cagliari.
- M. El-Demiry, MSc, PhD. Head of Department of Urology, Police Hospital, Cairo.
- G. Muscas, MD, Clinical Assistant, Department of Urology, Cagliari
- E. Usai, Professor and Head of Department of Urology, Cagliari.

Requests for reprints to: R. Migliari, Via Scano 18, 09129 Cagliari, Italy.

Transurethral Incision versus Transurethral Resection of the Prostate. A Subjective and Objective Analysis

P. F. SOONAWALLA and D. S. PARDANANI

Department of Urology, King Edward Memorial Hospital, Parel, Bombay, India

Summary—A prospective study was undertaken comparing transurethral incision of the prostate (TUIP) with transurethral resection (TURP) in the treatment of 220 patients with urinary obstruction caused by a small, benign prostate. Patients were managed alternately by TUIP and TURP, and their symptoms and urodynamic findings evaluated before and after surgery. Subjectively and objectively, the results were comparable in both groups. Pre- and post-operative complications were significantly less for the TUIPs than the TURPs. TUIP was significantly better than TURP in terms of shorter operating time, duration of hospitalisation and reduced need for transfusion. We recommend TUIP as the operation of choice for the relief of obstruction in the presence of a small, benign prostatic enlargement.

Transurethral resection of the prostate (TURP) is the preferred treatment for symptomatic benign prostatic hypertrophy in all but the largest of glands. Although advances in the technique and instrumentation have greatly reduced its morbidity and mortality, it remains, nevertheless, a major operative procedure, especially for the infrequent operator (Mebust *et al.*, 1989).

With the description of transurethral incision of the prostate in 1973 by Orandi, this technique has been increasingly used to treat small but obstructive prostates. Subsequently several reports have appeared in the literature testifying to the efficacy of this technique and reporting results matching those of TURP with fewer complications (Edwards and Powell, 1982; Hellstrom *et al.*, 1986; Orandi, 1987; Nielson, 1988). However, few studies compare the symptomatic relief and improvement in flow rates obtained following these 2 procedures in a prospective analysis of a large number of patients (Edwards *et al.*, 1985; Orandi, 1987). This report compares the results and complications of these 2 procedures in a prospective study of 220 patients.

Patients and Methods

A series of 220 patients presenting with prostatic hypertrophy were treated either by TUIP or TURP, with 110 patients randomly distributed in each group. Their ages ranged from 45 to 87 years, with a mean of 62.2 years among the TUIP group and 65.03 years among the TURP group. Pre-operative evaluation consisted of a complete haemogram, blood urea, creatinine, electrolytes and blood sugar estimations, chest X-ray, ECG and urine culture. Prostatic sizes as estimated on pre-operative cystoscopy combined with per-rectal examination were comparable in both groups of patients (Table 1). All patients with prostates larger than 30 g were excluded, as were those suspicious of malignancy.

Pre-operative uroflowmetry was performed on a 4-channel Uro-system 2100 micrometer from Dantek Electronics. Flow rates were corrected in relation to bladder capacity using the nomograms of Krane and Siroky (Blavias, 1979). The post-voiding residue was measured by catheterisation. Any residue > 20% of bladder capacity was considered significant (Stohrer and Heisler, 1989).

The incisions were conducted under spinal and general anaesthesia in 69 and 24 cases respectively. Seventeen TUIPs on patients who were deemed

high risk for other forms of anaesthesia were conducted under local anaesthesia using 1% lignocaine with 1:100,000 adrenaline added unless contraindicated. This was infiltrated periprostatically via the perineum, and submucosally along the line of the incision through the urethra. A single incision at the 5 or 7 o'clock position extending from below the ureteric orifice up to the verumontanum was made with the Collings' knife and deepened up to perivesical and periprostatic fat along its entire length. A few chips were resected from each lobe for histopathology. After haemostasis a 24 F Foley catheter was inserted on an introducer and kept in position for 24 to 48 h.

The TURPs were conducted under spinal (88 patients), general (20) and epidural anaesthesia (2). Resection was by the standard technique using a 24 F resectoscope. After haemostasis a 24 F Foley catheter was inserted and kept in position till the

urine became clear, usually up to 48 h. In both groups of patients the duration of the operative procedure, volume of irrigant used, volume of blood transfused and complications encountered were noted.

Follow-up ranged from a minimum of 3 months up to 2 years in both groups. Urine cultures were obtained at 1 week, 1 month and 3 months, or whenever indicated after surgery. Uroflowmetry and assessment of residue were repeated at 6 weeks, 3 months and 1 year post-operatively. Patients subjectively evaluated the results of the procedure as "excellent", "fair", "no change" or "worse". Statistical analysis of the results was done using the *t* test.

Results

The duration of the procedure, excluding the time required for anaesthesia, varied from 10 to 40 min for the TUIPs (mean 20.4) (Table 1). In comparison, the duration of TURPs ranged from 30 to 95 min (mean 59.2). The mean volume of irrigant used for TUIPs was 4.7 L compared to 15.9 L for the TURPs. Thirty-eight patients were transfused during or after TURP; the mean volume of blood given per patient was 0.44 units. In contrast, none of the incisions required transfusion. The details of the duration of catheterisation and post-operative hospitalisation are given in Table 1.

At follow-up 3 months post-operatively, average flow rates improved from a mean of 3.82 ml/s before TUIP to 11.32 ml/s after TUIP, and from 3.99 to 10.61 ml/s after resection (Table 2). Similarly, peak flow rates increased from 7.91 to 19.38 ml/s after TUIP and from 8.04 to 20.69 ml/s after TURP. The improvements following these 2

Table 1 Clinical Data

	TUIP (110)	TURP (110)
Mean prostatic weight (g)	14.8	15.6
Duration of surgery (min)		
mean	20.4	59.2
range	10-40	30-95
Volume of irrigant used (l)		
mean	4.7	15.9
range	2-12	7-28
Blood transfusion		
no. of patients	0	38
mean units per patient	0	0.44
Duration of catheterisation (days)	2.62	3.01
Duration of hospitalisation (days)	6.03	7.16

Table 2 Subjective and Objective Comparison between TUIP and TURP

	TUIP		TURP		TUIP		TURP	
	Pre-op	Post-operative	Pre-op	Post-operative	Pre-op	Post-operative	Pre-op	Post-operative
	(110)	3 months (110)	1 year (70)	2 years (26)	(110)	3 months (110)	1 year (67)	2 years (21)
Average flow rate (ml/s)	3.82	11.32	11.21	11.94	3.99	10.61	10.91	11.04
Peak flow rate (ml/s)	7.91	19.38	19.45	18.91	8.04	20.69	20.10	19.86
High residue	83 (73.5%)	8 (7.3%)	8 (7.3%)	8 (7.3%)	80 (72.7%)	9 (6.2%)	9 (6.2%)	9 (6.2%)
Satisfied (Excellent/fair)	—	105 (95.5%)	105 (95.5%)	105 (95.5%)	—	99 (90.0%)	99 (90.0%)	99 (90.0%)
Not satisfied (No change/worse)	—	5 (4.5%)	5 (4.5%)	5 (4.5%)	—	11 (10.0%)	11 (10.0%)	11 (10.0%)

procedures were statistically comparable. Eighty-three patients had significant residual volumes before, compared to 8 patients after TUIP. Similarly, 80 patients had high residues before TURP and only 9 patients after TURP. Subjectively, 95.5% of patients were satisfied after TUIP and 90% after TURP. These improvements following TUIP and TURP did not change significantly on follow-up 1 and 2 years post-operatively.

The TUR syndrome and serious haemorrhage or perforation requiring open surgery were commoner after TURP than TUIP (Table 3). Seven patients failed to void following removal of the catheter after TUIP, whereas 4 patients could not void after TURP. The other complications encountered are summarised in Table 3.

Only 60 patients who underwent TUIP and 49 who underwent TURP were sexually active at the time of surgery. Of these, ejaculation was lost in 14 (33%) of the incisions and in 13 (36%) of the resections. None of these patients lost erectile capacity. Malignancy was an incidental histological finding in 2 of the incisions and 3 of the resections.

Discussion

Since Orandi (1973) first described TUIP as a treatment for obstructive prostatic enlargement, numerous reports have appeared in the literature attesting to its efficacy (Edwards and Powell, 1982; Moisey *et al.*, 1982; Edwards *et al.*, 1985; Hellstrom *et al.*, 1986; Orandi, 1987). However, most studies are not randomised or do not include uroflowmetric analysis (Orandi, 1973; Edwards and Powell, 1982; Moisey *et al.*, 1982; Edwards *et al.*, 1985). This randomised prospective study compares the subjective

and objective improvement resulting from TUIP with that of TURP.

Although bilateral incisions were described by Orandi, others report equally good results with a single incision (Edwards and Powell, 1982; Moisey *et al.*, 1982; Edwards *et al.*, 1985; Hellstrom *et al.*, 1986). The present study confirms that a single incision gives results comparable to those of TURP. The average flow rate improved from 3.82 to 11.32 ml/s after TUIP and from 3.99 to 10.61 ml/s after TURP. The maximum flow rate increased from 7.91 to 19.38 ml/s after TUIP compared to 8.04 to 20.69 ml/s after TURP. There was no statistically significant difference between the 2 procedures. These results agree with those of Delaere *et al.* (1983) and Christensen *et al.* (1985), who reported comparable increases in flow rates after both procedures, with peak flow rates of 17.3 ml/s and 23 ml/s respectively after TUIP. In our series, residual volumes were significantly high (>20% of bladder capacity) in 83 patients before and in 8 patients after TUIP, compared with 80 patients before and 9 patients after TURP. Thus, residual volumes were significantly reduced in 90.36% of incisions and 88.75% of resections.

There was a comparable improvement in urodynamic parameters following incisions and resections. However, no technique can be declared a success unless the patient himself is satisfied with the results. In all, 95.5% of patients in this series were satisfied with the results of TUIP compared with 90% who were satisfied after TURP. This confirms the experience of Orandi (1987), Nielson (1988) and Edwards *et al.* (1985).

Of the 7 patients who failed to void after TUIP, in 4 the cause was an inadequate incision; all 4 were cured after a repeat incision. Three patients had lateral lobes prolapsing into the lumen of the urethra following the incision and required resection. After the TURP 4 patients could not void, of whom 2 required further resection and 2 were relieved after incision of the prostatic fossa. Serious haemorrhage and perforation requiring exploration were commoner following TURP. There was 1 death after TUIP from a myocardial infarct. Two deaths after resection were due to septicaemia and myocardial infarct. Table 3 shows that not only were complications more frequent, but there was a higher incidence of major complications following TURP. This was also the experience of Edwards *et al.* (1985).

Evaluation of sexual capability in this study was purely subjective. In no case was there a loss of erectile function after surgery. Of those patients

Table 3 Complications

	TUIP (110) (%)	TURP (110) (%)
<i>Intra-operative</i>		
TUR syndrome	0 (0.0)	7 (6.4)
Haemorrhage requiring open surgery	0 (0.0)	3 (2.7)
Perforation requiring open surgery	2 (1.8)	3 (2.7)
<i>Post-operative</i>		
Haemorrhage	0 (0.0)	2 (1.8)
Fever	12 (10.9)	14 (12.7)
Epididymo-orchitis	5 (4.5)	2 (1.8)
Acute renal failure	0 (0.0)	1 (0.9)
Stricture of the urethra	5 (4.5)	3 (2.7)
Failure to void	7 (6.4)	4 (3.6)
Incontinence	2 (1.8)	4 (3.6)
Death	1 (0.9)	2 (1.8)

who were sexually active before surgery, 33% were rendered an-ejaculate after TUIP and 36% after TURP. Although the use of a single incision has been reported to reduce the incidence of retrograde ejaculation compared with bilateral incisions or resection, this was seen neither in our study nor that of others (Turner-Warwick, 1979; Moisey *et al.*, 1982; Delaere *et al.*, 1983; Nielson, 1988).

In our experience, TUIP was a far easier procedure to learn and to teach. It was also much faster than the average resection (mean duration 20.4 and 59.2 min respectively). A considerable saving in terms of irrigating fluid used (mean volumes 4.7 L and 15.9 L for TUIP and TURP respectively) was also achieved. No patient required transfusion for an incision whereas 38 resections required transfusion, with a mean volume of 0.44 units per resection. With the threat of AIDS and other transmittable diseases this affords a considerable advantage. Though importance is given to brief hospitalisation in Western series, for social and other reasons this is not an important concern in India. The mean duration of hospitalisation was 6.03 days after TUIP and 7.16 days after TURP.

The study demonstrates the feasibility of performing TUIP using local anaesthesia. Although resections have also been reported under local anaesthesia, in our experience it is not a very reliable method. Eighteen incisions were successfully conducted under local anaesthesia of which only 1 required supplementation with intravenous ketamine.

The incidence of occult carcinoma following resection is reported to be between 0 and 20% (Catalona and Scott, 1986; Hellstrom *et al.*, 1986). Only 2 malignancies were detected following TUIP and 3 after TURP in this study. Edwards *et al.* (1985) reviewed 312 patients who had undergone TUIP up to 7 years previously and did not report any morbidity or mortality due to carcinoma. Orandi (1987) reported a 15% incidence of carcinoma in 132 incisions analysed after a period of up to 2 years. We advocate a thorough clinical examination and acid phosphatase assay pre-operatively, and resection of a few chips from each edge of the incision to provide a biopsy of the peripheral zone of the prostate. The use of transrectal ultrasound and PSA assays may also be useful to detect occult malignancies.

Patients in this series were followed up for up to 2 years but no late recurrence of obstruction was noted. The results of Edwards *et al.* (1985) and Orandi (1987) also suggest that the problem of recurrent obstruction after TUIP may be more a

theoretical possibility than a practical reality. On the basis of these results we strongly advocate transurethral incision of the prostate as the operation of choice for the relief of obstruction by a small, benign prostatic enlargement.

References

- Blalvas, J. G. (1979). A critical appraisal of specific diagnostic techniques. In *Clinical Neuro-urology*, ed. Krane R. J. and Siroky, M. B. First edition. Chapter 5, pp. 69–109. Boston: Brown and Co.
- Catalona, W. and Scott, W. W. (1986). Carcinoma of the prostate. In *Campbell's Urology*, ed. Walsh, P. C., Gittes, R. F., Perlmutter, A. D. and Stamey, T. A. Fifth edition. Chapter 32, pp. 1463–1554. Philadelphia: Saunders.
- Christensen, M. G., Nordliag, J., Andersen, J. T. *et al.* (1985). Functional bladder neck obstruction. Results of endoscopic bladder neck incision in 131 consecutive patients. *Br. J. Urol.*, **57**, 60–62.
- Delaere, K. P. J., Debruyne, F. M. J. and Moonen, W. A. (1983). Extended bladder neck incision for outflow obstruction in male patients. *Br. J. Urol.*, **55**, 225–228.
- Edwards, L. E., Bucknall, T. E., Pittam, M. R. *et al.* (1985). TUR of the prostate and bladder neck incision; a review of 700 cases. *Br. J. Urol.*, **57**, 168–171.
- Edwards, L. and Powell, C. (1982). An objective comparison of transurethral resection and bladder neck incision in the treatment of prostatic hypertrophy. *J. Urol.*, **28**, 325–327.
- Hellstrom, P., Lukkarinen, O. and Kontturi, M. (1986). Bladder neck incision or transurethral electroresection for the treatment of urinary obstruction caused by a small, benign prostate. *Scand. J. Urol. Nephrol.*, **20**, 187–192.
- Mebust, W. K., Holtgrewe, H. L., Cockett, A. T. K. *et al.* (1989). Transurethral prostatectomy: immediate and post-operative complications. A cooperative study of 13 participating institutions evaluating 3885 patients. *J. Urol.*, **141**, 243–248.
- Moisey, C. U., Stephenson, T. P. and Evans, C. A. (1982). A subjective and urodynamic assessment of unilateral bladder neck incision for bladder neck obstruction. *Br. J. Urol.*, **54**, 114–117.
- Nielson, H. O. (1988). Transurethral prostatotomy versus transurethral resection of prostate in benign prostatic hyperplasia. A prospective randomised study. *Br. J. Urol.*, **61**, 435–438.
- Orandi, A. (1973). Transurethral incisions of the prostate. *J. Urol.*, **110**, 229–231.
- Orandi, A. (1987). Transurethral incision of prostate compared with transurethral resection of prostate in 132 matching cases. *J. Urol.*, **138**, 810–815.
- Stohrer, M. and Heisler, W. (1989). *Urodynamic Handbook* Wiest, GmbH & Co.
- Turner-Warwick, R. (1979). A urodynamic review of bladder outlet obstructions in the male and its clinical applications. *Urol. Clin. North Am.*, **6**, 171–192.

The Authors

P. F. Soonawalla, MS, MCh, DNBE (Urol), Lecturer.
D. S. Pardanani, MS, FACS, FAMS, Professor and Head of Department of Urology.

Requests for reprints to: P. F. Soonawalla, Ness Bag 2, Nana Chowk, Bombay 400 007, India.

Localised Deep Microwave Hyperthermia in the Treatment of Benign Prostatic Hyperplasia: Long-term Assessment

A. YERUSHALMI, D. SINGER, R. KATSNELSON, E. LEVY and A. SHANI

Department of Cell Biology, Weizmann Institute of Science; Clinical Hyperthermia Unit, Department of Urology and Oncological Institute, Kaplan Hospital, Rehovot, Israel

Summary—A group of 133 patients with benign prostatic hyperplasia who were either poor operative risks or who had refused surgery underwent localised deep microwave hyperthermia, without supplementary drugs. In 59% of patients who had had an indwelling catheter, freedom from urological obstruction and satisfactory voiding were maintained for 7 years and catheterisation was not required. In patients with severe prostatic symptoms, 65% showed general improvement and satisfactory voiding for 8 years.

There were no side effects. Patients who relapsed were given a second course of treatment and 75% responded positively.

This positive response and the lack of side effects suggest that localised deep microwave hyperthermia may be an effective alternative to surgery in the management of high risk patients and those who are reluctant to undergo surgery.

Benign prostatic hyperplasia (BPH) is the commonest neoplastic disease in man. The increase in prostatic volume and the morphological incidence of BPH with age are well established (Franks, 1954). There is no effective conservative management and the only effective treatment is either transurethral or open prostatectomy, but in many cases this is contraindicated by the patient's advanced age and/or other diseases (Walsh, 1979; De Klerk, 1983). These considerations led us to develop the technique of localised deep microwave hyperthermia, thus permitting non-surgical treatment of BPH without side effects.

Local hyperthermia (LH), combined with radiotherapy or chemotherapy, has been used for the last 3 decades in the treatment of a variety of tumours in man (Corry *et al.*, 1980; Noell *et al.*, 1980; Engelhardt, 1987). To date, most data on hyperthermia as treatment for cancer relate to patients at an advanced stage of the disease, allowing only short-term follow-up. No information on the long-term response has been available.

In 1980 we began to treat BPH with LH. Since neither sedation nor anaesthesia was required, it was possible to treat patients on an out-patient basis. The first clinical results were reported by Yerushalmi *et al.* (1985) and our techniques and protocol have been adopted by others (Servadio *et al.*, 1986; Lindner *et al.*, 1987, 1990). Treatment of BPH with LH has also taken the form of transurethral hyperthermia (Astrahan *et al.*, 1989).

In the last 3 years LH has been used more often for the treatment of BPH and its efficacy has been firmly established (Baert *et al.*, 1990; Lindner *et al.*, 1990; Strohmaier *et al.*, 1990; Wada *et al.*, 1990; Zerbib *et al.*, 1990).

We report our experience in the treatment of BPH with local hyperthermia over a period of 10 years.

Patients and Methods

The study was carried out on 133 patients; 89 had severe prostatic symptoms and 44 had either bladder outflow obstruction or >150 ml residual urine requiring an indwelling catheter for 1 to 10

months prior to treatment. During this period, up to 4 attempts to dispense with catheterisation had failed. Patients with urethral strictures were excluded from the study. Prostatectomy was indicated in all cases, but patients either refused or were unable to undergo surgery because of other diseases.

Local hyperthermia was proposed as an alternative to surgery. The method of treatment, protocol and the limitations of the clinical trial were explained to each patient and they were included after giving written consent. Before and after treatment, patients were assessed by routine urological investigations, *i.e.* imaging (IVU or ultrasound), physical examination (including digital palpation of the prostate), biochemistry (neural function tests, urine analysis and culture) and other tests (measurement of residual urine and flow rates, cystoscopy and prostate biopsy). Since the study covered a 10-year period, it should be noted that ultrasound and accurate flow measurements were implemented during this time and not all patients were diagnosed by these techniques.

Symptom analysis was based on the patient's account of the quality of the urinary stream, hesitancy, urgency, nocturia and frequency.

A symptom score system (Table 1) was designed to assess the benefit of treatment (Jensen *et al.*, 1983). The total obstructive symptom score was calculated by combining the individual scores. The therapeutic gain ratio of treatment was the ratio of the post-treatment to the pre-treatment total score. Clinical status was graded as 3 for a ratio of over 50% post-treatment to pre-treatment total score, 2 for a ratio of 30 to 50% and 1 for a ratio of less than 30%. Standardised forms for data collection and analysis formed the basis of the evaluation.

At follow-up the same evaluation was repeated at monthly intervals for the first 3 months and at 6-monthly intervals thereafter.

Treatment

Localised hyperthermia, at 42.5 to 43°C, was delivered by a transrectal applicator operating at

2.45 Ghz. The applicator was equipped with a cooling system to avoid overheating of the rectal mucosa and rectal wall, which were maintained at 32°C or lower (Yerushalmi *et al.*, 1985; Yerushalmi, 1986, 1988). The temperature of the prostatic mass could not be measured non-invasively and so invasive temperature measurements were not performed routinely. The intratumour temperature was evaluated by an algorithm based on accumulated temperature measurements confirmed by invasive temperature measurements (Yerushalmi *et al.*, 1985). The algorithm's validity was confirmed by invasive temperature measurements (Wada *et al.*, 1990).

Hyperthermia treatments were given twice weekly in 12 to 16 sessions, each lasting 1 h on an out-patient basis, without sedation, anaesthesia or supplementary drugs.

Results

The treatment was well tolerated by all patients and there were no acute or long-term side effects, no damage to the rectal mucosa or rectum and no irritative voiding symptoms. For evaluation purposes the patients were divided into 2 groups.

Group 1 comprised 89 patients without a catheter whose severe prostatic symptoms were treated with local hyperthermia; 82 were assessed (Table 2) using the assessment and symptom scoring system previously described. According to the symptom score, 80% of these patients benefited from a single treatment. Objectively, peak flow rates increased by an average of 27% (from 8.2 to 10.4 ml/s), with an average mean flow rate increase of 23% (from 4.2 to 5.2 ml/s). Residual urine measurements after treatment were <100 ml (average 67) compared with a pre-treatment average of 86 ml. There was no significant change in prostate size as determined by digital palpation and ultrasound.

In 65% of patients the improvement persisted for 8 years. The condition of 13% of patients who

Table 1 Symptom Score Scale

Scale	Frequency	Nocturia	Quality of urinary stream	Urgency	Hesitancy
0	Normal voiding	0	Good	None	None
1	Mild frequency ($\times 2-3/h$)	$\times 1$	Satisfactory	Mild	Mild
2	Moderate frequency ($\times 1.5-2/h$)	$\times 2-3$	Weak	Mild	Mild
3	Severe frequency ($\times 1/h$)	$\times 4-5$	Poor	Severe	Severe
4	Very severe ($\times 15-30/min$)	> 5			

showed an initial response to treatment deteriorated and they were referred for surgery.

Since no side effects were observed, patients who relapsed were given a second course of hyperthermia; 83% responded positively and in 65% this improvement persisted (Table 3).

The second group consisted of 44 patients with bladder outflow obstruction who required an indwelling catheter for 1 to 10 months prior to

treatment. After treatment, 66% of these patients were able to dispense with their catheter and had spontaneous micturition, with residual urine <100 ml (Table 4). Their flow rates, after treatment, were comparable to those in the first group.

During a follow-up period of up to 7 years, 59% of patients maintained satisfactory voiding, while 7% of those who showed an initial response regressed to their pre-treatment condition; their

Table 2 Clinical Response of Patients without a Catheter

<i>Clinical status after treatment*</i>				<i>Clinical status 8 years after treatment*</i>			
1	2	3	Failed (%)	1	2	3	Failed (%)
45	35	15	5	41	24	14	21
Total improvement 80%				Total improvement 65%			

No. of patients: 89. Non-evaluable: 7. Age range 50–85 years (mean 74).

No. of sessions 8–20 (mean 12) Follow-up period 0.5–8 years (mean 4.7).

*See Methods.

Table 3 Clinical Response of Patients receiving 2 Courses of Treatment

<i>First Course</i>				<i>Second course</i>		
<i>Age (years)</i>	<i>No of sessions</i>	<i>Clinical status*</i>	<i>Months to 2nd course</i>	<i>No of sessions</i>	<i>Clinical status after treatment*</i>	<i>Clinical status months () after treatment*</i>
73	15	1	9	11	2	2† (16)
71	14	2	79	14	2	2 (15)
74	7	1	51	9	2	3 (5)
65	11	2	9	9	1	2 (32)
73	15	1	3	13	3	3 (25)
84	10	3	8	11	2	2† (2)
75	7	2	24	9	2	2 (13)
74	11	2	29	7	2	3 (17)
75	16	3	7	10	3	2† (15)
62	8	1	7	9	2	3 (26)
72	9	1	18	9	2	1 (18)
76	11	3	22	10	2	2 (2)

*See Methods †Died

Table 4 Clinical Status of Patients with Catheters

<i>Clinical status of catheter-free patients after treatment (residual urine <100 ml)*</i>				<i>Clinical status 7 years after treatment*</i>		
1	2	3	Failed (%)	1	2	Failed (%)
54	6	6	34	43	16	41
Total catheter-free 66%				Total catheter-free 59%		

No. of patients: 44 Non-evaluable: 7. Age range 59–86 years (mean 73) No. of sessions 6–20 (mean 13) Follow-up period 0.5–7 years (mean 4.2)

*See Methods.

residual urine exceeded 150 ml and regular catheterisation was required (Table 4).

Fifteen patients from both groups died between 2 and 51 months after treatment (Table 5). In each case a single course of local hyperthermia had provided effective relief until their death.

Discussion

Since its introduction by Young (1905), prostatectomy has been a source of debate with regard to morbidity and mortality. It was concluded that transurethral prostatectomy (TURP) patients run a higher long-term risk of mortality than those undergoing open prostatectomy (Roos *et al.*, 1989). Both methods are invasive and cannot be used in poor risk patients.

The aim of the present study was to evaluate the efficacy of local hyperthermia in the treatment of BPH. Our first report (Yerushalmi *et al.*, 1985) and subsequent communications (Yerushalmi, 1986, 1988) confirmed the safety of the procedure and established it as an additional form of treatment for BPH.

In contrast to oncological hyperthermia, where disease-free survival is not yet a realistic aim, the aetiology and character of BPH permit long-term

evaluation of disease-free patients. Since the mechanism of action of hyperthermia on benign and malignant tumours is not completely understood, we present only a clinical evaluation of the efficacy of this treatment.

BPH is multifocal in histology and genesis. The progressive, although remittent, course of the disease from its initial onset to the end stage of acute retention, may evolve over many years and varies from patient to patient (Castro, 1974; Birkhoff *et al.*, 1976). During much of this time the patient is unaware of the process until the disease is manifested clinically. Symptoms include nocturia, impairment of the urinary stream, frequency, sensation of incomplete emptying, hesitancy, intermittency and terminal dribbling. Clinical manifestation of the disease starts when the size of the enlarged prostate exceeds a critical volume above which obstruction occurs. This critical volume is different for each patient. Thus the final obstructing mass in a patient with a small prostate may be larger than that in a patient with a large one.

Rectifying the obstruction, therefore, does not necessarily require elimination of the whole prostatic mass, but only a decrease in prostate volume below the critical obstructing mass. A small reduction in the volume of an initially large prostate, not clearly detectable by sonography, may be enough to provide symptomatic relief. Assessment of prostatic volume before and after treatment is thus not necessarily a marker for the efficacy of treatment. Spontaneous urine flow and little or no residual urine are more relevant criteria for judging the success or failure of treatment.

Patients referred for hyperthermia in this study were either not suitable for surgery, and local hyperthermia was the only alternative treatment, or they had refused surgery. There was no randomised selection of patients but those with indwelling catheters served as their own control, since previous attempts to dispense with catheterisation had failed.

Patients who died within the follow-up period represent the focal group in this project, since they died of diseases which did not permit surgical treatment. They were free of urological obstruction during their remaining life span. The ability to repeat the treatment, and the positive results obtained from so doing, indicate the possibility of long-term management of the disease in poor operative risk patients.

In conclusion, this decade of experience indicates that local hyperthermia, without supplementary drugs, may provide alternative, non-surgical treat-

Table 5 Clinical Status of Patients who Died from Diseases which Contraindicated Surgery

Age (years)	Catheter (months)	Contraindication*	No. of sessions	Status† (survival in months)
76	+(3)	1,2,5	10	C F (18)
86	+(2)	1,8	19	C F (17)
71	+(10)	5,6,10	10	C.F. (8)
69	+(1)	1,9	11	C.F. (5)
61	+(2)	7,10,12	6	C.F. (2)
72	—	5,6,11	10	1(51)
73	—	1,2,4,11	11	2(48)
78	—	2	11	3(43)
72	—	5,11	11	1(31)
72	—	1	10	2(25)
76	—	7	19	2(24)
74	—	12	10	2(20)
77	—	2,3,7	11	1(13)
76	—	1	16	3(7)
82	—	1,3,11,13	10	2(3)

*1. Past and recent myocardial infarction. 2. Anginal syndrome. 3. Hypertension. 4. Sick sinus syndrome. 5. Congestive heart failure. 6. Chronic obstructive lung disease. 7. S.A. Cerebrovascular accident. 8. S.A. Pulmonary oedema. 9. Ventricular tachycardia. 10. Chronic atrial fibrillation. 11. Ischaemic heart disease. 12. Poor general condition. 13. Severe Parkinson's disease. †As detailed in Methods. C.F. = Catheter-free. S.A. = State After

ment for BPH patients who are unsuitable for surgery or who are reluctant to undergo operative treatment.

References

- Astrahan, M. A., Sapozink, M. D., Cohen, D. *et al.* (1989). Microwave applicator for transurethral hyperthermia of benign prostatic hyperplasia. *Int J. Hyperthermia*, **5**, 283–296.
- Baert, L., Ameye, F., Willemen, P. *et al.* (1990). Transurethral hyperthermia for BPH and prostatodynia: preliminary clinical and pathological results. *Strahlenther. Onkol.*, **166**, 507.
- Birkhoff, J. D., Wiederhorn, A. R., Hamilton, M. L. *et al.* (1976). Natural history of benign prostatic hypertrophy and acute urinary retention. *Urology*, **7**, 48–52.
- Castro, J. E. (1974). *The Treatment of Prostatic Hypertrophy and Neoplasia*. Pp. 40–45. Baltimore: University Park Press.
- Corry, P., Barlogie, B., Spanos, W. *et al.* (1980). Approaches to clinical applications of nonionizing and ionizing radiations. In *Radiation Biology in Cancer Research*, ed. Meyn, R. E. and Withers, H. R. Pp. 637–644. New York: Raven Press.
- De Klerk, D. P. (1983). In *Benign Prostatic Hypertrophy*, ed. Hinman F. Pp. 262–270. New York, Heidelberg, Berlin: Springer-Verlag.
- Engelhardt, R. (1987). Hyperthermia and drugs. In *Hyperthermia and the Therapy of Malignant Tumours*, ed. Streffer, C. Pp. 236–293, Berlin: Springer-Verlag.
- Franks, L. M. (1954). Benign nodular hyperplasia of the prostate: a review. *Ann R. Coll. Surg.*, **14**, 92–97.
- Jensen, K. M. E., Bruskewitz, P. C., Iversen, P. *et al.* (1983). Abdominal straining in benign prostatic hyperplasia. *J. Urol.*, **129**, 44–48.
- Lindner, A., Braff, Z., Lev, A. *et al.* (1990). Local hyperthermia of the prostate gland for the treatment of benign prostatic hypertrophy and urinary retention. *Br. J. Urol.*, **65**, 201–204.
- Lindner, A., Golomb, J. and Lev, A. (1987). Local hyperthermia of the prostate gland for the treatment of benign prostatic hypertrophy and urinary retention. *Br. J. Urol.*, **60**, 567–571.
- Noell, U. R., Woodward, K. T., Worde, B. T. *et al.* (1980). Microwave-induced local hyperthermia in combination with radiotherapy of human malignant tumors. *Cancer*, **45**, 638–646.
- Roos, N. P., Wennberg, J. E., Malenka, D. J. *et al.* (1989). Mortality and reoperation after open and transurethral resection of the prostate for benign prostatic hyperplasia. *N. Engl. J. Med.*, **320**, 1120–1124.
- Servadio, C., Leib, Z. and Lev, A. (1986). Further observations on the use of local hyperthermia for the treatment of diseases of the prostate in man. *Eur. Urol.*, **12**, 38–41.
- Strohmaier, W. L., Bichler, K. H. and Fluchter, S. H. (1990). Micturition parameters in patients with BPH before and after hyperthermia. *Strahlenther. Onkol.*, **166**, 534.
- Wada, S., Yasumoto, R., Kawano, M. *et al.* (1990). The experience of the transrectal hyperthermia for treating BPH. *Strahlenther. Onkol.*, **166**, 538.
- Walsh, P. C. (1979). Benign prostatic hyperplasia. In *Campbell's Urology*, ed. Harrison, J. H., Gittes, R. F., Perlmutter, A. D., Stamey, T. A. and Walsh, P. C. Pp. 949–964. Philadelphia: Saunders.
- Yerushalmi, A., Fishelovitz, Y., Singer, D. *et al.* (1985). Localized deep microwave hyperthermia (LDMW) in the treatment of poor operative risk patients with benign prostatic hyperplasia. *J. Urol.*, **133**, 873–876.
- Yerushalmi, A. (1986). Hyperthermia treatment of prostate tumors. In *Hyperthermia in Cancer Treatment*, ed. Anghileri, L. and Robert, J. Pp. 89–101. Boca Raton, Florida: CRC Press.
- Yerushalmi, A. (1988). Localized, non-invasive deep microwave hyperthermia for the treatment of prostatic tumours: the first 5 years. *Recent Results Cancer Res.*, **107**, 141–146.
- Young, H. H. (1905). The early diagnosis and radical cure of carcinoma of the prostate, being a study of 40 cases and presentation of radical operation which was carried out in 4 cases. *Bull. Johns Hopkins Hosp.*, **16**, 315–317.
- Zerbib, M., Steg, A., Comquy, S. *et al.* (1990). A prospective randomized study of localized hyperthermia vs. placebo in obstructive benign hypertrophy of the prostate. *Strahlenther. Onkol.*, **166**, 540.

The Authors

- A. Yerushalmi, PhD, Radiation Consultant, Weizmann Institute of Science; Head, Clinical Hyperthermia Project, The Kaplon Hospital.
- D. Singer, MD, Attending Urologist, Department of Urology and Clinical Hyperthermia Unit, The Kaplon Hospital.
- R. Katsnelson, MD, Physician, Oncological Institute, The Kaplon Hospital.
- E. Levy, MD, Senior Physician, Oncological Institute, The Kaplon Hospital.
- A. Shani, MD, Head, Oncological Institute, The Kaplon Hospital.

Requests for reprints to: A. Yerushalmi, Department of Cell Biology, Weizmann Institute of Science, Rehovot 76100, Israel.

Inter-relation between Measurement of Serum Prostatic Specific Antigen and Transrectal Ultrasound in the Diagnosis of Benign Prostatic Hyperplasia and Prostatic Cancer

R. CLEMENTS, R. J. ETHERINGTON, G. J. GRIFFITHS, W. B. PEELING, H. HUGHES
and M. D. PENNEY

Departments of Radiology, Urology and Chemical Pathology, Royal Gwent Hospital, Newport

Summary—Serum prostatic specific antigen (PSA) and ultrasound-determined prostatic volume (UPV) were measured in 50 patients with histologically proven benign prostatic hyperplasia (BPH) and in 40 patients with histologically proven prostatic cancer of whom 17 had evidence of distant metastases (M1) and 23 did not (M0).

A good correlation between log PSA and UPV was demonstrated in the BPH group and rearrangement of the linear regression equation allowed calculation of a single variable—the log PSA corrected to a standard prostate volume for any given individual.

A volume-corrected PSA correctly identified all patients with M1 disease and greatly improved but did not eliminate overlap of M0 disease with BPH. Reduction of serum PSA to a single volume-corrected variable will allow the introduction of practical and optimum protocols for the management of patients with prostatic enlargement.

During the past decade there have been major developments in 2 types of investigation used in the assessment of prostatic disease, namely the serum assay for prostatic specific antigen (PSA) and the use of transrectal ultrasound imaging (TRUS). Both techniques have been of considerable value, both separately and in combination, in the diagnosis and management of prostatic cancer.

Prostatic specific antigen is a glycoprotein of 33 kilodaltons found only in the cytoplasm of prostatic epithelial cells: the primary structure of PSA has been established which suggests it is a serum protease of the kallikrein group of proteins (Watt *et al.*, 1986). A role in the liquefaction of semen has been suggested (Lilja, 1985).

The measurement of PSA in serum appears to offer a significant improvement over serum prostatic acid phosphatase as a marker for prostatic cancer. Several applications of the measurement of

PSA have been proposed in the management of patients with prostatic cancer: as an aid to the staging of established disease, for monitoring response to treatment, and potentially for the screening and early detection of prostatic cancer (Killian and Ming Chu, 1990). Both benign hyperplasia and carcinoma may, however, cause a rise in PSA levels (Rainwater *et al.*, 1990); large rises normally indicate prostatic malignancy and cause few problems, but there may be difficulty with the interpretation of smaller elevations when there is coexisting benign hyperplasia. The use of PSA as an initial clinical screen for prostatic cancer has been limited by this false positive elevation produced by benign prostatic hyperplasia. It is necessary, therefore, to allow for the presence of benign hyperplasia when interpreting the result of the assay.

The establishment of a normal reference range for PSA has been problematic because, without careful histological examination of the entire

prostate, the absence of carcinoma, benign hyperplasia or other pathology cannot be excluded. Given the high prevalence of asymptomatic carcinoma as well as benign hyperplasia, the absence of clinical signs of either disease does not preclude their existence. In addition, any procedure that causes significant prostatic tissue injury such as urethral instrumentation, prostatic surgery or biopsy, or vigorous prostate massage, may result in elevation of PSA (Stamey *et al.*, 1987; Vesey *et al.*, 1988).

It is increasingly common for patients to be referred for prostatic ultrasound because of an elevated PSA level. Recent improvements in ultrasound equipment have enhanced image resolution and have enabled small hypoechoic areas to be defined. Interpretation of such areas may be difficult and decisions about the need for prostatic biopsy may be influenced by the PSA level. The problem for the clinician and ultrasonologist is particularly related to small elevations of PSA. As the volume of the prostate may influence the level of serum PSA it is with small elevations that a correction for prostatic volume may be most helpful.

Transrectal ultrasound is an extremely accurate method of measuring prostatic volume (Clements *et al.*, 1989) and the measurement of serum PSA is both robust and precise. We have, therefore, determined the influence of ultrasound-determined prostatic volume on serum PSA in patients with histologically proven benign prostatic hyperplasia, and in patients with proven prostatic cancer, to establish a practical way of providing volume-corrected PSA data for clinical interpretation and decision.

Patients and Methods

The PSA measurement and UPV in 2 groups of patients have been analysed retrospectively. In the first group of 50 patients the gland was considered benign by both digital rectal examination and transrectal ultrasound scan. Subsequently a transurethral resection of the prostate was undertaken and histological examination of the resected specimens demonstrated benign prostatic hyperplasia with no evidence of malignancy. In the second group of 40 patients, prostatic malignancy was proven by histological examination of specimens obtained either by prostatic biopsy or transurethral resection. These patients were divided into 2 subgroups (M0, M1) according to the presence or absence of distant metastases as assessed by chest radiographs and radioisotope bone scans.

In all patients the PSA and UPV measurements were obtained within 4 weeks of each other. The PSA measurements were performed using a 2-site immunoradiometric assay (Hybritech Inc.). The ultrasound examinations were undertaken with a Bruel and Kjaer 1846 scanner with either a 4MHz radial transducer or a 7MHz multiplanar transducer. All volume measurements were obtained by planimetry by measuring the area of the gland at 0.5-cm intervals and summing the areas to obtain a measurement of prostatic volume. The relationship between serum PSA and UPV in benign prostatic hyperplasia was analysed by Deming regression analysis, a method of linear regression which takes into account the precision of measurement of both variables (Cornbleet and Gochman, 1979).

Results

The results for prostatic volume and PSA were heavily skewed and did not conform to gaussian distributions for any group of patients.

The 50 patients with benign prostate glands were aged between 53 and 86 years (mean 72). The volume varied from 8 to 244 ml (mean 62); the serum PSA levels varied from 1.3 to 85 µg/l (mean 7.7). There was a highly significant correlation between serum PSA and UPV in the benign group, with the best correlation between log transformed PSA and non-transformed UPV (Fig. 1). The regression equation was as follows:

$$\text{Log PSA} = 0.00562 (\text{UPV}) + 0.32$$

$$r = 0.62$$

SD of residual error of regression about $Y = 0.30$

PSA = serum prostatic specific antigen (µg/l)

UPV = ultrasound prostatic volume (ml).

The 40 patients with prostatic cancer were divided into 2 subgroups (M0, M1) according to the presence or absence of distant metastases: there were 23 patients with M0 disease aged 55 to 90 years (mean 73) and 17 patients with M1 disease aged 53 to 83 years (mean 65). For patients with M0 disease the UPV ranged from 9 to 151 ml (mean 49) and the serum PSA concentration varied from 3.8 to 720 µg/l (mean 97.5). For patients with M1 disease the UPV ranged from 17 to 62 ml (mean 38) and the PSA concentration from 47 to 6890 µg/l (mean 1337). None of the 12 patients with

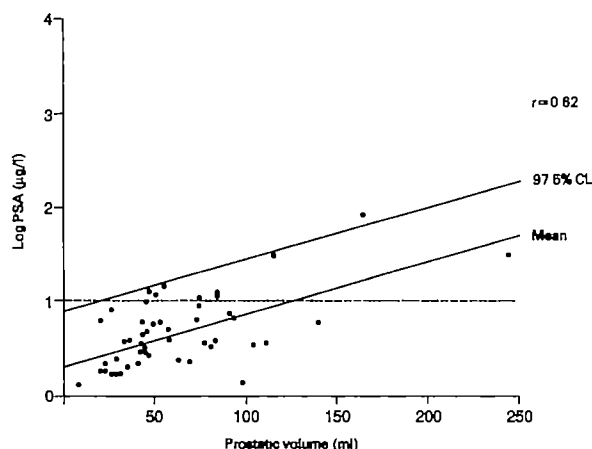


Fig. 1 Prostatic volume and log PSA measurements in 50 patients with histologically confirmed benign prostate glands

- a PSA measurement below $45 \mu\text{g/l}$ had M1 disease. The results for patients with prostatic cancer are illustrated in Figure 2 with the mean and 97.5% upper confidence limit (CL) for patients with benign disease incorporated.

Discussion

- Although the measurement of PSA in serum has been available using commercial assays for the past 7 years, there is continuing controversy over the reference range or action range when the measurement is used to assess patients with clinically diagnosed benign prostatic hyperplasia. Part of the problem is the proof of the benign nature of the hyperplasia and part is the relationship of serum PSA level to the volume of benign prostatic tissue. Both benign and malignant tissue contribute to the serum PSA level but the relative contributions from each are different and are greater with respect to malignant tissue by a ratio of approximately 10:1 (Stamey and Kabalin, 1989). Since benign hyperplasia and prostatic cancer are most prevalent during the same age range in life, the influence of hyperplastic tissue on the serum PSA concentration must be known if PSA is to be a useful marker for prostatic cancer. In addition, both disease processes may coexist in the same patient, and this can be a further problem in the interpretation of the PSA result.

The need to use the PSA measurement, interpreted with respect to prostatic volume, has recently been explored in a screening programme involving 764 self-referred patients (Littrup *et al.*, 1991a). These authors grouped ultrasonically measured

gland volumes into quartiles and ascribed mean PSA levels and 95th percentiles for each quartile. Although this introduces an element of volume correction for serum PSA it lacks precision at the edges of the quartiles, and by its definition does not address the correction of large volume prostates ($> 50 \text{ ml}$). The log-linear regression equation of serum PSA versus UPV provides the ultrasonologist with a method of volume correction for serum PSA. The correction of serum PSA for UPV may be obtained by plotting the result and graphically relating to the upper 97.5% CL (Fig. 1). Such a graph may be kept for reference in clinics, wards and the scanning room, and it can be quickly ascertained whether a PSA value lies outside the 97.5% CL for benign glands for a particular measurement of gland volume.

Alternatively, a single variable may be derived; a serum PSA value at a standard prostatic volume

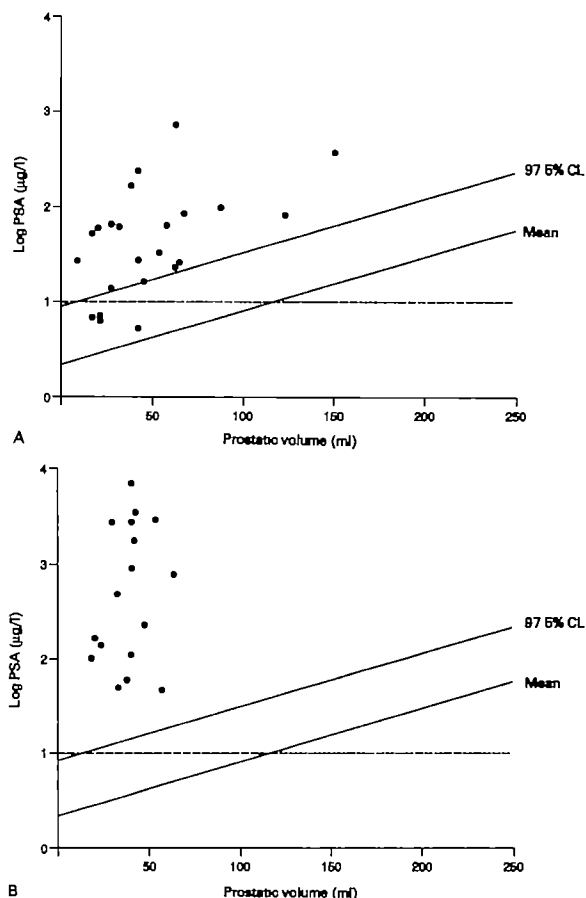


Fig. 2 Prostatic volume and log PSA measurements in 40 patients with prostatic cancer. The mean relationship and 97.5% upper confidence limit for benign glands (derived from Fig. 1) has been added. (A) 23 patients with M0 cancer. (B) 17 patients with M1 cancer

such as 50 ml (PSA₅₀) can be calculated by using the slope of the Deming regression equation.

Thus

$$\text{Log PSA}_{50} = \text{Log PSA} + 0.00562 (50\text{-UPV})$$

Where

$$\text{Log PSA} = \text{Log serum PSA result } (\mu\text{g/l})$$

$$\text{Log PSA}_{50} = \text{Corrected Log PSA result to a standard UPV of 50 ml.}$$

Thus Mean Log PSA₅₀ for the benign group under study

$$= 0.601 (97.5\% \text{ CL } 1.196)$$

$$= 4.0 \mu\text{g/l} (97.5\% \text{ CL } 15.7).$$

Any PSA₅₀ measurement exceeding 15.7 $\mu\text{g/l}$ would therefore be strongly suspicious of malignancy, although the exact working cut-off used in any screening procedure would depend on the optimum efficiency and predictive values required with respect to the prevalence of prostatic malignancy in the population under study (Galen and Gambino, 1975). If it is decided to use PSA₅₀ values, it may be possible to have a small alteration incorporated into the software program of the ultrasonic scanner, so that PSA₅₀ value can be calculated from the serum PSA level for the particular measured volume and be displayed on the scanning monitor alongside the volume measurement. It should be emphasised also that interpretation of serum PSA levels will depend on the type of assay used: there is as yet no internationally agreed standard for PSA and controversy exists on the relative specificities of commercially available assays (Yang, 1988). Furthermore, the method of assessing UPV is crucial to any analysis and different methods give differing results (Littrup *et al.*, 1991b; Terris and Stamey, 1991). Theoretically it might be more accurate to relate PSA to the volume of the ultrasonic transition zone (TZ), *i.e.* the volume of the adenoma of BPH, but in our experience it has not yet been practical to obtain reliable objective measurements of TZ volume with ultrasound. Finally, although the influence of the rectal examination (digital or ultrasound) on transiently elevating serum PSA is small (Hughes *et al.*, 1987), this should be avoided by obtaining serum samples for PSA measurement either from ambulatory out-patients prior to such examinations (Stamey *et al.*, 1987), or following at least 5 $\times$ the beta phase half-life of PSA (this approximates to a minimum of 11 days following such examinations).

Prostatic volume has an important effect on the

interpretation of the serum PSA levels and this is particularly important in the assessment of small elevations of PSA, *e.g.* up to 20 $\mu\text{g/l}$. A volume-corrected serum PSA value will aid the urologist in his clinical assessment of the gland and has relevance to ultrasonologists undertaking prostatic ultrasound scanning and biopsy of the prostate. Biopsy of the prostate may be undertaken simply by the transrectal route with minimal complication using a spring loaded biopsy device, *e.g.* the Biopsy gun (Toz-Pedersen and Lee, 1989). It is now agreed that the majority of cancers originate in the peripheral zone of the prostate, but that central zone and transition zone cancers do also occur (McNeil *et al.*, 1988). It is also agreed that most (but not all) cancers are hypoechoic (Lee *et al.*, 1985; Griffiths *et al.*, 1987). In ultrasonological practice there may be doubt about whether a hypoechoic area visualised by TRUS should be biopsied, and knowledge of the PSA could influence this decision. The following examples illustrate areas where optimal protocols for biopsy and follow-up are not yet established for patients undergoing prostatic ultrasound and where knowledge of the serum PSA may influence management by the ultrasonologist.

1. A small (<0.7 cm) hypoechoic area in the peripheral zone.
2. Larger hypoechoic areas in the peripheral zone with benign previous biopsy.
3. Transition zone hypoechoic areas in a patient with an ultrasonically normal peripheral zone.
4. The isoechoic gland.

Knowledge of a volume-corrected PSA should be of value to urologists and radiologists in establishing their management protocols for these patients.

Screening programmes to detect early prostate cancer are in progress in both American and European centres based on various combinations of digital rectal examination, serum PSA measurement and transrectal ultrasound. An understanding of the effect of prostatic volume on the PSA measurement will be particularly important to ensure that these programmes, involving very large numbers of patients, operate in an efficient and cost-effective manner.

References

- Clements, R., Griffiths, G. J., Peeling, W. B. *et al.* (1989) Transrectal ultrasound in monitoring response to treatment of prostatic disease *Urol. Clin. North Am.*, **16**, 735-740.

- Cornbleet, P. J. and Gochman, N. (1979). Incorrect least-squares regression coefficients in method comparison analysis. *Clin. Chem.*, **25**, 432-438.
- Galen, R. S. and Gambino, S. R. (1975). *Beyond Normality. The Predictive Value and Efficiency of Medical Diagnosis* Pp 34-36. New York: Wiley.
- Griffiths, G. J., Clements, R., Jones, D. R. *et al.* (1987). The ultrasonic appearances of prostatic cancer with histological correlation. *Clin. Radiol.*, **38**, 219-227.
- Hughes, H. R., Peamey, M. D., Ryan, P. G. *et al.* (1987). Serum prostatic-specific antigen: *in vitro* stability and the effect of ultrasound rectal examination *in vivo*. *Ann. Clin. Biochem.*, **24**, S1-206-207.
- Killian, C. S. and Ming Chu, T. (1990). Prostate-specific antigen: questions often asked. *Cancer Invest.*, **8**, 27-37.
- Lee, F., Gray, J. M., McLeary, R. D. *et al.* (1985). Transrectal ultrasound in the diagnosis of prostate cancer: location, echogenicity, histopathology and staging. *Prostate*, **7**, 117-129.
- Lilja, H. (1985). A kallikrein-like serine protease in prostatic fluid cleaves the predominant seminal vesicle protein. *J. Clin. Invest.*, **76**, 1899-1903.
- Littrup, P. J., Kane, R. A., Williams, C. R. *et al.* (1991a). Determination of prostate volume with transrectal US for cancer screening Part I. Comparison with prostate specific antigen assays. *Radiology*, **178**, 537-542.
- Littrup, P. J., Williams, C. R., Egglin, T. K. *et al.* (1991b). Determination of prostate volume with transrectal US for cancer screening Part II: Accuracy of *in vitro* and *in vivo* techniques. *Radiology*, **179**, 49-53.
- McNeill, J. E., Redwine, E. A., Freiha, F. S. *et al.* (1988). Zonal distribution of prostatic adenocarcinoma. Correlation with histologic pattern and direction of spread. *Am. J. Surg. Pathol.*, **12**, 897-906.
- Rainwater, L. M., Morgan, W. R., Klee, G. G. *et al.* (1990). Prostate-specific antigen testing in untreated and treated prostatic adenocarcinoma. *Mayo. Clin. Proc.*, **65**, 1118-1126.
- Stamey, T. A. and Kabalin, J. N. (1989). Prostatic specific antigen in the diagnosis and treatment of adenocarcinoma of the prostate. I. Untreated patients. *J. Urol.*, **141**, 1070-1075.
- Stamey, T. A., Yang, N., Hay, A. R. *et al.* (1987). Prostate-specific antigen as a marker for adenocarcinoma of the prostate. *N. Engl. J. Med.*, **317**, 910-916.
- Terris, M. K. and Stamey, T. A. (1991). Determination of prostate volume by transrectal ultrasound. *J. Urol.*, **145**, 984-987.
- Torp-Pedersen, S. T. and Lee, F. (1989). Transrectal biopsy of the prostate guided by transrectal ultrasound. *Urol. Clin. North Am.*, **16**, 703-712.
- Vesey, S. G., Goble, N. M., Stower, M. J. *et al.* (1988). The effects of transurethral prostatectomy on serum prostate specific antigen. *Br. J. Urol.*, **62**, 347-351.
- Watt, K. W. K., Lee, P. J., Thnkulu, T. M. *et al.* (1986). Human prostate-specific antigen: structural and functional similarity with serine proteases. *Proc. Natl. Acad. Sci.*, **83**, 3166-3170.
- Yang, N. (1988). Endogenous antibody to prostate-specific antigen in women. *Clin. Chem.*, **34**, 647-648.

The Authors

- R. Clements MA, FRCS, FRCR, Consultant Radiologist, Royal Gwent Hospital.
- R. J. Etherington, FRCR, formerly Senior Registrar in Radiology, Royal Gwent Hospital. Now Consultant Radiologist, Countess of Chester Hospital, Chester.
- G. J. Griffiths, MD, FRCR, Consultant Radiologist, Royal Gwent Hospital.
- W. B. Peeling, MA, FRCS, Professor of Urological Surgery and Consultant Urological Surgeon, St Woolos Hospital, Newport.
- H. Hughes, BSc, MSc, Principal Biochemist, Royal Gwent Hospital.
- M. D. Penney, BSc, MD, MRCPath, Consultant Chemical Pathologist, Royal Gwent Hospital.

Requests for reprints to: R. Clements, Department of Radiology, Royal Gwent Hospital, Newport, Gwent NP9 2UB.

Laparoscopic Ligation of Internal Spermatic Vein

MING-TSUN CHEN, ALLEN WEN-HSIANG CHIU and LUKE S. CHANG

Division of Urology, Department of Surgery, National Yang-Ming Medical College, Veterans General Hospital, Taipei, Taiwan, Republic of China

Summary—Laparoscopic procedures have long been a standard form of treatment for gynaecological disorders but have only recently shown promise in the evaluation and treatment of urogenital diseases, such as pelvic lymphadenectomy. We performed laparoscopic ligation of the bilateral internal spermatic veins in 15 male pigs. The average operative time was 20 min and operative morbidity was minimal, comprising mild subcutaneous emphysema around the trocars. Engorgement of the spermatic vein proximal to the endoclip site was noted. There was no operative mortality. Laparoscopic ligation of the internal spermatic veins seems to be a feasible method for the treatment of varicoceles, especially bilateral lesions.

Since Kelling (1923) first used a cystoscope to observe the intra-abdominal organs of a dog, several authors have advanced the clinical applications of laparoscopy (Jacobaeus, 1923; Ruddock, 1937). Despite the efforts of these early investigators, laparoscopy was adopted by only a few surgeons, mainly in Europe. It was only after the advent of laparoscopic cholecystectomy that general surgeons became interested in laparoscopy. In the field of endourology, transperitoneal endosurgical lymphadenectomy in patients with localised prostate cancer was successfully performed with minimal morbidity and an acceptable level of complications (Schuessler *et al.*, 1991).

At present, interruption of venous reflux by surgical methods is the most effective treatment for varicocele patients. The elimination of venous reflux to the engorged pampiniform plexus can be performed either inguinally or retroperitoneally by an open surgical technique. The surgical scar and the time required to approach the internal spermatic veins are unavoidable. For patients with bilateral varicoceles, the same operation must be performed in 2 different sites. In an attempt to reduce operating time and to minimise tissue injury, we performed laparoscopic ligation of the bilateral internal spermatic veins in the pig to evaluate its potential for clinical application.

Materials and Methods

Fifteen male pigs, aged 3 months and weighing 18–20 kg, were studied. They were housed in cages each containing 2 animals; they had free access to water and were fed standard pig food. Each animal was pre-treated with intramuscular ketamine (10 mg/kg). Surgery was conducted under intraperitoneal pentobarbital anaesthesia (30 mg/kg). Endotracheal intubation and a ventilator were set up prior to the surgical procedure. Urethral catheterisation was necessary in order to empty the urinary bladder. The operation field was sterilised with aqueous Betadine. Prior to insertion of the trocars, the table was adjusted to a 15° Trendelenburg tilt. Insufflation was accomplished with a Veress needle placed above the umbilicus. The needle was inserted with the tip angled slightly toward the symphysis. The abdominal wall was elevated with a towel clip to avoid visceral injury by the needle. A 10-ml syringe containing isotonic saline was attached to the Veress needle and the fluid level was observed as it fell due to gravity in order to confirm the accurate location of the needle tip. The carbon dioxide insufflator was then connected to the Veress needle. The inflow pressure was kept below 15 mmHg, the flow usually exceeding 1 litre per min. Approximately 2.5 litres were needed to distend the peritoneal cavity. The contour of the abdomen and abdominal percussion were further

guidelines to confirm accurate insufflation. The needle was then removed and an 11-mm trocar inserted into the abdomen through the supra-umbilical site. The trocar was positioned in the palm of the right hand, with the back of the trocar against the thenar eminence. The second finger protruded down the shaft of the trocar, preventing the instrument from being inserted too far. The abdominal wall was elevated with 2 towel clips on either side of the umbilicus prior to insertion of the initial trocar. A 10-mm lens was inserted, with camera and light cord attached, allowing initial inspection of the abdominal cavity. The camera was colour-adjusted before insertion. The intra-abdominal organs, including the urinary bladder, suspensory ligament of the bladder, colon, internal inguinal rings, vas deferens, iliac vessels, ureter and spermatic vessels, were inspected first. After orientation was accomplished, 2 accessory trocars, 5 mm in size, were inserted under direct vision midway between the umbilicus and the anterior superior iliac spine on either side of the abdomen. Two grasping forceps were used to approach the left spermatic vessels first. These vessels could be traced easily from the internal ring. The site of dissection of the spermatic vessels was approached as proximally as possible. The internal spermatic artery and internal spermatic veins could be distinguished by their external appearance, the artery being pink-red in colour and the vein dark red. The spermatic vein was also distinguished by its proximal engorgement when clamped with the grasping forceps for a short time. The overlying peritoneum was opened by sharp dissection with scissors and the spermatic veins were easily isolated with forceps. An endoclip was applied to the spermatic vein. After ligation, there was immediate engorgement of the vein proximal to the clip. The right internal spermatic veins were ligated in a similar manner. After ligation, the operative fields were inspected for haematoma. If there was no evidence of bleeding, insufflation was stopped. The 3 trocars were removed after emptying the abdominal cavity. The fascia over the umbilical incision was closed with 3/0 polyglycolic acid sutures and the skin was closed with 3/0 nylon. The endotracheal tube was removed, and the pigs returned to their cage after resuming normal respiration.

Results

The pigs tolerated the procedure well and bleeding was minimal. The average time taken for bilateral vein ligation was 20 min from the setting up of the

trocar to wound closure. Immediate engorgement of the internal spermatic vein proximal to the endoclip was noted in all pigs. Operative morbidity was minimal. Respiratory impairment was noted when peritoneal insufflation began before endotracheal intubation was well established. Mild subcutaneous emphysema was found around the trocar site and this slowly subsided post-operatively. There was no operative mortality.

Discussion

Despite the lack of scientific data to compare laparoscopy with traditional open operations, laparoscopic surgery has gained rapid acceptance and implementation (Dent, 1991). No other technological advance has attracted such widespread attention and debate as laparoscopic cholecystectomy (Olsen, 1991). Laparoscopic cholecystectomy is an alternative to standard cholecystectomy and offers the patient a shorter stay in hospital, with discharge usually less than 24 h post-operatively, a faster return to work, with unrestricted activities possible in less than 7 days, and improved cosmetic results (Olsen, 1991). These advantages also apply to laparoscopic pelvic lymphadenectomy and other laparoscopic procedures.

In 1889, Bennett operated on a patient with bilateral varicocele and found an objective improvement in semen quality after surgery. Traditional surgical treatment for bilateral varicocele often involves 2 different operative sites. The approach to the internal spermatic vein can be made by either the inguinal or the retroperitoneal route. The time taken to perform the operation and the damage to tissue are a matter of concern to both patients and physicians. A human cadaver study shows that the spermatic vein has a unique, fixed course where it divides into 2 sections, medial and lateral. The medial division anastomoses before its termination with the ureteric veins and cross-communicates with the other spermatic vein at the level of L3. The lateral division anastomoses with the colonic and renal capsular veins before its termination in perinephric fat. The bifurcation of the 2 main trunks is at L4, and below this level is the ideal site for percutaneous occlusion of the vein (Wishahi, 1991). Thus venous reflux and recurrence are both prevented. It is therefore logical to ligate the spermatic vein at the internal inguinal ring laparoscopically.

Subclinical varicoceles have attracted attention recently. A varicocele is characterised by distension of the pampiniform plexus within the scrotum.

However, when retrograde blood reflux occurs and the scrotal venous plexus is not yet palpably distended the varicocele will not be located clinically. McClure *et al.* (1991) reported that patients with subclinical varicoceles showed an improvement in sperm motility post-operatively as frequently as did patients with clinical varicoceles. This finding is in accord with the accepted belief that the size of the varicocele does not influence the surgical outcome. It appears that detection and treatment of subclinical varicoceles may be warranted in infertile men with abnormal semen analysis. We consider that subclinical varicoceles may be detected more accurately by means of testicular colour Doppler ultrasonography (Petros *et al.*, 1991). It is reasonable to look for contralateral subclinical varicoceles with Doppler ultrasonography in every varicocele patient. We have described a new approach using the laparoscope in the treatment of bilateral varicoceles, whether clinical or subclinical. The average duration of the procedure, including setting up the trocars and wound closure, was approximately 20 min and operative morbidity was minimal. The technique is not difficult for any endourologist with experience of laparoscopic procedures.

In conclusion, we believe that laparoscopic ligation of the internal spermatic veins is a feasible method for the treatment of varicocele, especially bilateral lesions.

Acknowledgements

We thank Mr Seng-wong Huang and Miss Chu Chun-lien for their invaluable technical assistance.

References

- Bennett, W. H. (1889). Varicocele, particularly with reference to its radical cure. *Lancet*, **1**, 261–263.
- Dent, T. L. (1991). Training, credentialling, and granting of clinical privileges for laparoscopic general surgery. *Am. J. Surg.*, **161**, 399–403.
- Jacobaeus, H. C. (1923). Kurze Übersicht über meine Erfahrungen mit der Laparoskopie. *Munch. Med. Wochenschr.*, **58**, 2017–2019.
- Kelling, G. (1923). Zur Coelioskopie. *Arch. Klin. Chir.*, **126**, 226–229.
- McClure, R. D., Khoo, D., Jarvi, K. *et al.* (1991). Subclinical varicocele: the effectiveness of varicocelectomy. *J. Urol.*, **145**, 789–791.
- Olsen, D. O. (1991). Laparoscopic cholecystectomy. *Am. J. Surg.*, **151**, 339–344.
- Petros, J. A., Andriole, G. L., Middleton, W. D. *et al.* (1991). Correlation of testicular color Doppler ultrasonography, physical examination and venography in the detection of left varicoceles in men with infertility. *J. Urol.*, **145**, 785–788.
- Ruddock, J. C. (1937). Peritoneoscopy. *Surg. Gynecol. Obstet.*, **65**, 623–639.
- Schneeder, W. W., Vancallie, T. G., Reich, H. *et al.* (1991). Transperitoneal endosurgical lymphadenectomy in patients with localized prostate cancer. *J. Urol.*, **145**, 988–991.
- Wishah, M. M. (1991). Detailed anatomy of the internal spermatic vein and the ovarian vein. Human cadaver study and operative spermatic venography: clinical aspects. *J. Urol.*, **145**, 780–784.

The Authors

Ming-Tsun Chen, MD, Associate Professor of Urology; Chief, Division of Urology.

Allen Wen-Hsiang Chiu, MD, Instructor of Urology, Visiting Staff, Division of Urology.

Luke S. Chang, MD, Professor of Urology, Chairman, Department of Surgery.

Requests for reprints to: Allen Wen-Hsiang Chiu, Division of Urology, Department of Surgery, Veterans General Hospital-Taipei, No. 201, Section 2, Shih-Pai Road, Taipei, Taiwan, Republic of China.

Urine Transparency as an Index of Absence of Infection

GABRIELLE PHILLIPS, LAURA W. FLEMING, I. KHAN and W. K. STEWART

Department of Medical Microbiology, Department of Medicine, and Renal Unit, Ninewells Hospital and Medical School, University of Dundee, Dundee

Summary—A visual assessment of the clarity of urine was used as an exclusion test to indicate the absence of infection; verified by dipslide culture, it was applied to 363 urine samples collected from patients attending 2 adult nephrology clinics over a period of 6 months. The crimped aluminium bowl used for collection of samples assisted the assessment of clarity. The sensitivity of the method compared with dipslide culture was 73%, with specificity and efficiency both 58%.

The predictive value of a negative test (clarity) was 97% with a false negative rate of 3%, enabling this simple examination to be used as an exclusion test for further testing. In simple terms, a clear urine is unlikely to be infected. It is also an advantage to have an immediate indicator of the absence of infection available at the clinic. Analysis of only those urines assessed as cloudy could result in financial savings and, from the clinics, a 56% reduction in workload.

Although the chemical testing of urine was said to have started with Richard Bright's evaluation of urinary protein in nephritis, the image of a medieval physician inspecting urine in a glass is quite familiar to most doctors. One possible aim was to determine the transparency (clarity) or otherwise of the urine, irrespective of colour. The urine of healthy adults consuming a meat- and fish-based diet is invariably clear after voiding. While loss of clarity may occasionally indicate microhaematuria, it usually indicates the presence of diffusely dispersed white cells concomitant with infection.

Urine culture has become a major workload for many clinical bacteriology laboratories. Samples are taken from widely differing groups of patients, often without careful instruction on avoiding contamination. Transport to the laboratory may be suboptimal, with delay allowing overgrowth of contaminants. Ninewells Hospital serves a population of 200,000 and urine samples constitute 43% of the total annual workload in the bacteriology

department, of which around 30% are reported as significant growths. Current costs quoted per examination of urine specimens range from £1.30 (Edmondson and Shread, 1990) to £5 (Rawal *et al.*, 1990), depending on the numbers received and on how much associated activity (computer time, secretarial time, overheads and consumables, *etc*) is included.

A simple screening method at the clinic level to reduce the number of negative specimens submitted for bacteriological culture would be cost-saving and would enable laboratory staff to devote more time to abnormal samples. Cloudiness or loss of clarity involves interference or blurring of patterns inspected through urine. The depth of the urine sample is itself an important, independent influence and should be stated. In an attempt to predict the absence of infection, we have studied the usefulness as an exclusion test of simple visual inspection of clarity in freshly passed, warm urine samples between 2 and 5 cm deep, collected in sterile disposable aluminium bowls which are supplied for mid-stream urine collecting.

Patients and Methods

Samples of urine ($n = 363$) were collected according to usual practice from virtually all patients (120 males and 107 females, mean age 51 years, range 12–85) attending morning renal out-patient clinics, held on 2 consecutive days each week, for approximately 6 months. All patients, most of whom were asymptomatic, were asked to provide "a clean catch, middle of the stream sample". Catheter urine samples were not included in this study.

The sample of urine, collected directly into the aluminium bowl, was examined by 1 of 4 staff nurses. The specimen was graded as "clear" (perfectly transparent) or "cloudy" (loss of transparency irrespective of degree). The criterion used was the sharpness of the metal folds in the wall of the bowl below as compared with above urine surface level. Inspection was carried out in bright daylight, when the reflections of ambient light from the sides of the bowl helped interpretation. Particulate material, such as inadvertent debris, does not change the entire background clarity of urine and was not equated with cloudiness.

A dipslide culture (Medical Wire and Equipment Co, UK) was obtained from the same bowl and the results of the culture were compared with the results of the inspection. For the purposes of this evaluation, the results of the dipslide culture were taken as the "gold standard". Pure bacterial growths of $> 10^4$ colony-forming units (cfu) per ml urine were regarded as indicative of infection. Samples in which more than one organism was isolated were interpreted as being suggestive of faecal contamination and counted as not infected.

Results

Of the 363 specimens inspected, 202 (56%) were classified as clear and 161 (44%) as cloudy (Table 1). Six of the clear urines and 16 of the cloudy urines were subsequently found to have $> 10^4$ cfu/ml of a pure growth of organisms on culture. The incidence of infection (22/363 samples) over the period of study was therefore low (6%). Of the cloudy urines, 145 were negative on culture. Accordingly, the sensitivity of visual inspection (true positives in the diseased) and its specificity (true negatives in the healthy) were not particularly high (73% and 58% respectively).

On the other hand, the predictive value of a negative test (Table 2) was high (97%) and the false negative rate was low (3%), which implies that the test is suitable as an exclusion test. Only 6 of the negative results were not true negatives (27% of those with positive culture). Of the 6 patients with clear urines and significant bacteriuria (4 females and 2 males), all but 1 male were asymptomatic. All 4 females grew *Escherichia coli*. In 1 case the records were incomplete and it is not known if antibiotics were prescribed. Of the other 3 patients, 1 (F79, steroid-sensitive nephrotic syndrome) received no antibiotic treatment and subsequent cultures were normal; another (F65, glomerulonephritis) was given antibiotics for chest symptoms, and the third (F61, analgesic nephropathy) received no treatment but was given antibiotics 4 weeks later at the next clinic visit, when both symptoms and cloudy urine were evident. Both male patients received antibiotics. One suffered from chronic pyelonephritis, complained of loin pain, *Escherichia*

Table 1 Results of Clarity Testing of Urine in Renal Clinics, Compared with the Presence or Absence of Dipslide Culture Infection

	Culture positive	Culture negative	Totals
Clinic 1			
Cloudy urine (a b)	5	27	32
Clear urine (c d)	3	69	72
Clinic 2			
Cloudy urine (a b)	11	118	129
Clear urine (c d)	3	127	130
Overall			
Cloudy urine (a b)	16	145	161
Clear urine (c d)	6	196	202
Overall totals	22	341	363

a = true positives, b = false positives, c = false negatives, d = true negatives

Table 2 Parameters of Urine Clarity as an Exclusion Test, Compared with Other Screening Methods

Test patients' samples (n)	This report clinic		All	Flanagan et al. (1989)	Rawal et al. (1989)	Pouchot et al. (1989)	See A to F * 1988-89 Multi-dipsticks (various combinations)	Flanagan et al. (1989)	Goldsmith and Campos (1990)	
	I 104	2 259		363	Elderly 418	Children 376	Adult medical 134	Mixed 500-2000	Elderly 418	Children 1010
Clarity										
Clarity										
Test patients' samples (n)										
Sensitivity (a/a+c)%	63	79	73	90	—	71	54-97	89-97	21-76	
Specificity (d/d+b)%	72	52	58	66	—	86	38-94	18-79	81-99	
Positive predictive value (a/a+b)%	16	8	10	64	—	37	26-67	45-69	—	
Negative predictive value (d/d+c)%	96	98	97	91	99	96	93-99	91-94	95-98	
False negatives in culture positive (c/c+a)%†	37	21	27	10	—	29	3-46	3-11	24-79	
False positives in culture negative (b/b+d)%‡	28	48	42	34	—	14	6-62	21-82	1-19	
False positive rate (b/b+a)%§	84	92	90	36	—	63	33-74	31-55	—	
False negative rate (c/c+d)%¶	4	2	3	9	1	4	1-7	6-9	2-5	
Efficiency (a+d/a+b+c+d)%	71	63	58	—	—	84	48-87	—	—	

* (A) Smith *et al.* (1988); (B) Doran and Kensit (1989); (C) Coia and Wills (1989), (D) Medcraft and Stacey (1989); (E) Levy *et al.* (1989); (F) Pezzlo *et al.* (1989)

† Opposite of sensitivity

‡ Opposite of specificity

§ Opposite of positive predictive value

¶ Opposite of negative predictive value

coli was cultured and he responded well to antibiotics. The other male suffered from microscopic polyarteritis and was being treated with immunosuppressive drugs. The urine sample grew *Salmonella enteritidis* PT₄ and he responded well to a course of oral ciprofloxacin.

The overall efficiency of the test (correct results compared with dipstick culture) was 58% (Table 2). The specificity and efficiency of the test were higher in Clinic 1 (72% and 71% respectively) than in Clinic 2 (51% and 53% respectively), where the nursing staff seemed less sure of clarity. The predictive value of a negative test remained high, however, and the false negative rate was lower than in Clinic 1.

Discussion

It is suggested that the clarity criterion would be a justifiable preliminary screening procedure for asymptomatic patients, *i.e.* those who do not complain of dysuria, increased frequency of micturition or visible change in the character or odour of the urine, but in whom occult urinary tract infection could be relevant. This might apply in paediatric, geriatric, psychiatric, antenatal and renal patients. In renal clinics the decision is often made to send a sample for culture "just in case". Moreover, visual inspection at the clinic has the advantage of encouraging the clinician or nurse to react to the presence of other macroscopic changes. Even with less efficient recognition of clarity, the test remains of practical value. The only drawback to a less confident recognition of clarity is that more urines are sent for culture. The high false positive rate and low predictive value of positive results (*i.e.* cloudiness) are not significant clinically as the cloudy samples are all sent for culture. So, apart from cost, which could be reduced even further if the false positive rate were lower, the test has a sufficiently high predictive value for negative results (clarity equated with health) to be both useful and cost-effective. Even allowing for the high false positive rate, the use of this test as an exclusion screen at the clinic could reduce the urine culture workload at the laboratory considerably. Christenson *et al.* (1985) suggested that urine clarity should be used as the final criterion in a screening chain, whereas we believe that clarity could be used as the initial criterion.

From the results quoted in Table 2, it can be seen that both assessment of clarity and all of the other dipstick screening tests tend to have high negative predictive values and low false negative rates,

whatever the sensitivity or specificity. Clarity assessment, which costs nothing, is as good as the various dipstick methods in this respect. The lower sensitivity of the clarity assessment reflects the fact that more dipstick culture-positive samples are missed, but this may not be relevant clinically as some of these apparent infections will be false positive on culture and some will clear spontaneously without treatment.

Rawal *et al.* (1990) (Table 2) examined the clarity of urine from children by inspection of 5 to 10 ml urine in a universal container held up against a plain white background. However, the curvature of the glass wall of a universal container acts as a crude lens and makes focusing through the sample difficult. The advantage of our method is that the sharp lines of the many folded ridges of the crimped aluminium bowl aid assessment of clarity. Use of this bowl also saves transfer of urine into a second receptacle for testing. We agree with Rawal *et al.* (1990) that the examination of freshly voided urine for clarity, applied by them to paediatric nephrology and accident and emergency clinics, is also applicable to adult nephrology clinics. Its adoption would result in substantial savings to the Health Service.

Pouzhot *et al.* (1990) (Table 2) examined the clarity of urines from adults attending an internal medicine clinic and found higher degrees of sensitivity, specificity and predictive value for a positive test than we did, but the same high predictive value for a negative test (96%). Nevertheless, they concluded that the clarity test was not useful and preferred the screening recommended by Flanagan *et al.* (1989), which included dipstick tests for nitrite, leucocyte esterase, protein and blood. In order to function as an exclusion test, however, it is the high predictive value of a negative result, combined with a low false negative rate, that is of value.

Hook (1990) emphasised the importance of symptoms and found large numbers of clear urines in an asymptomatic population (*e.g.* the elderly, children, or pregnant women) unremarkable. He objected to applying clarity testing to a wide range of disparate clinics. However, patients are not always reliable in terms of symptomatology and renal patients may have more than one cause for urinary frequency if not dysuria; thus examination of samples from both symptomatic and asymptomatic patients has to be done.

Doran and Kensit (1988) rejected the Clinitec-200 dipsticks for blood, nitrite and leucocyte esterase because they missed 9% of those with

positive cultures (91% sensitivity). Our simple clarity test missed a quarter of those with positive cultures (73% sensitivity) but we conclude that in clinics with a low incidence of infection (6%), where the emphasis is on excluding non-infected urines as opposed to identifying infected ones, a simple and almost cost-free exclusion test has a valid place and can usefully be applied to all asymptomatic patients. Urine from symptomatic patients would be cultured anyway.

It is not suggested that clarity testing alone should be used as a criterion for initiating antibiotic treatment. Its value lies firstly in its usefulness as a screening test for avoiding further unnecessary investigation and secondly in the provision of an immediately available and easily repeatable result. Careful instruction of the nurses as to what constitutes urine clarity should result in a reduction in the high false positive rate and even further savings. Skill in the assessment of clarity and appreciation of the concept can be gradually acquired. We suggest that further ward and clinic surveys should be undertaken in order to assess the applicability of clarity testing in other specialities.

Acknowledgement

The authors thank the nursing staff of the 2 clinics involved for their careful assessments.

References

- Christenson, R. H., Tucker, J. A. and Allen, E. (1985). Results of dipstick tests, visual inspection, microscopic examination of urine sediment, and microbiological culture of urine compared for simplifying urinalysis. *Clin. Chem.*, **31**, 448-450.
- Coia, J. E. and Wills, G. (1989) Dipstick urinalysis for bacteriuria. *J. Clin. Pathol.*, **42**, 444.
- Doran, H. M. and Kensit, J. G. (1988). Screening for bacteriuria with Clinitec-200. *J. Clin. Pathol.*, **41**, 1127-1129.
- Edmondson, S. G. and Shread, P. (1990). Significance of crystal clear urine. *Lancet*, **I**, 321.
- Flanagan, P. G., Rooney, P. G., Davies, E. A. *et al.* (1989). Evaluation of four screening tests for bacteriuria in elderly people. *Lancet*, **I**, 117-119.
- Goldsmith, B. M. and Campos, J. M. (1990). Comparison of urine dipstick, microscopy and culture for the detection of bacteriuria in children. *Clin. Pediatr. (Phila.)*, **29**, 214-218.
- Hook, E. B. (1990) Significance of crystal clear urine. *Lancet*, **I**, 321.
- Levy, M., Tournot, F., Muller, C. *et al.* (1989) Evaluation of screening tests for urinary infection in hospital patients. *Lancet*, **II**, 384-385.
- Medcraft, J. and Stacey, A. (1989). Clinitec 200 as a screening test for bacteriuria. *J. Clin. Pathol.*, **42**, 780.
- Pezzo, M. T., Ige, V., Woolard, A. P. *et al.* (1989). Rapid bioluminescence method for bacteriuria screening. *J. Clin. Microbiol.*, **27**, 716-720.
- Pouchot, J., Lamay, I., Cahen, P. *et al.* (1990) Significance of crystal clear urine. *Lancet*, **I**, 320-321.
- Rawal, K., Senguttuwan, P., Morris, M. *et al.* (1990). Significance of crystal clear urine. *Lancet*, **I**, 1228.
- Smith, T. K., Hudson, A. J. and Spencer, R. C. (1988). Evaluation of six screening methods for detecting significant bacteriuria. *J. Clin. Pathol.*, **41**, 904-909.

The Authors

- Gabrielle Phillips, MB,ChB, MRCPATH, Consultant, Medical Microbiology and Virology, Department of Medical Microbiology.
- Laura W. Fleming, BSc, Senior Scientific Officer, Department of Medicine.
- I Khan, MB,ChB, MRCP, Registrar, Renal Dialysis Unit.
- W. K. Stewart, MD, PhD, FRCP, FRCPE, Reader, Department of Medicine

Requests for reprints to: Laura W. Fleming, Department of Medicine, Ninewells Hospital and Medical School, Dundee DD1 9SY.

PAEDIATRIC UROLOGY

Current Management of Duplex-System Ureterocele: Experience with 41 Patients

A. M. K. RICKWOOD, I. REINER, M. JONES and C. POURNARAS

Regional Department of Paediatric Urology, Royal Liverpool Children's Hospital (Alder Hey), Liverpool

Summary—Experience is described of 41 infants and children with duplex-system ureterocele, 25 presenting clinically and 16 by prenatal ultrasonography. Bladder outflow obstruction was rare but lower polar vesicoureteric reflux (VUR), usually of lesser grades, was common. Upper polar function, as assessed by ^{99m}Tc -DMSA, was negligible in children with truly ectopic ureterocele but well preserved in those where the lesion lay wholly intravesically. Lower polar function was good, even in the presence of secondary obstruction, except in 2 infants with major VUR.

Twenty-three patients were treated by upper polar nephrectomy plus aspiration of the ureterocele; 2 subsequently required ureterocele excision. Histology of excised specimens indicated that a more conservative approach would not have been rewarded. Where upper polar function was good, conservation was maintained in 3 cases by pyelopyelostomy and in 5 more by excision of the ureterocele plus bipolar ureteric reimplantation. Other operative strategies were employed in 2 cases. Finally, a defined group of 8 children was managed expectantly without untoward results.

It was concluded that the variable anatomy and function associated with duplex-system ureterocele require a flexible approach to treatment, including, possibly, no treatment at all.

The management of duplex-system ureterocele continues to attract a measure of controversy that doubtless reflects the variations of anatomy and renal function with which they are associated. Although these lesions are usually synonymously termed ectopic ureterocele, implying encroachment to or beyond the bladder neck, a proportion are situated wholly intravesically. Truly ectopic lesions may cause bladder outflow obstruction, especially if the ureterocele is tense. Function of the affected upper renal poles varies from little at all to perfect preservation. Vesicoureteric reflux to the lower renal pole is common, though seldom severe, and may be associated with congenital dysplasia or with acquired renal scarring. Less often, a tense ureterocele may cause secondary obstruction of the lower polar ureter, with or

without impairment of polar function. Lastly, bladder outflow obstruction may cause global dilatation of the upper renal tracts, leading in severe cases to permanently compromised overall renal function. Symptoms are similarly diverse and range from a life-threatening combination of septicaemia and azotaemia to none whatever. The latter has become common with the advent of prenatal ultrasonography.

It would seem to be generally accepted that these lesions always merit surgical intervention, regardless of severity or mode of presentation, and until recently such treatment has concentrated upon the ureterocele itself, either in the form of endoscopic incision (Tank, 1980; Gerridzen and Schillinger, 1984) or operative excision combined with lower polar ureteric reimplantation and, usually, simultaneous (Kroovand and Perlmutter, 1979) or subsequent (Johnston and Johnson, 1969) upper polar nephrectomy. Because excision of truly ectopic

ureterocele is not without difficulty or hazard (Williams and Woodward, 1965), especially where the bladder is thick-walled due to outflow obstruction, it has more recently been advocated that initial treatment be addressed to the upper renal pole, with excision where function is poor or pyelopyelostomy where useful function remains (King *et al.*, 1983; Caldamone *et al.*, 1984). In either case, the ureterocele itself is collapsed by aspiration via the distal ureteric remnant, so relieving any bladder outflow obstruction or secondary obstruction of the lower polar ureter. Also, it is claimed that this policy makes for easier excision of the ureterocele should this later prove necessary.

It is our contention that the variable nature and presentation of duplex-system ureterocele call for a flexible approach and that while most recommended strategies have merit in individual cases, none is universally applicable. In addition, our experience leads us to question whether some cases require surgical intervention at all.

Patients and Methods

All of the patients reviewed here presented with duplex-system ureterocele from 1984 to 1990 inclusive. Ultrasonography was the usual initial investigation, followed in most cases by IVU and cystoscopy. As a rule, ^{99m}Tc dimercaptosuccinic acid (DMSA) scintigraphy was undertaken to assess

polar function. Where initial treatment was directed to the upper renal pole, cystography was performed after, rather than before, such intervention. When other approaches were adopted, cystography formed part of the initial investigative regimen.

Results

The study group comprised 41 patients (29 females, 12 males) whose ages at presentation ranged from birth to 6 years (mean 1.1 year); 23 presented with urinary infection, 16 by prenatal ultrasonography and 1 each with urinary retention and with urinary ascites. Three had bilateral lesions and a further 3 had non-concordant contralateral duplex-system anomalies (1 each urethral ureteric ectopia, introital ureteric ectopia, lower polar VUR).

Among the 44 lesions, 29 encroached to or beyond the bladder neck, including 1 prolapsing; 9 lay wholly intravesically and 6, where cystoscopy was not performed, were unknown. Thirty-five patients were assessed by ^{99m}Tc -DMSA scintigraphy: upper polar function was negligible or absent in 29 instances (Fig. 1) and normally preserved in 6 (Fig. 2), all with intravesical lesions. Of the 23 patients who underwent cystography prior to any surgical intervention, 15 had ipsilateral lower polar VUR (4 grade I, 7 Grade II, 4 Grade III) (International Reflux Study Committee, 1981); in 2 of these

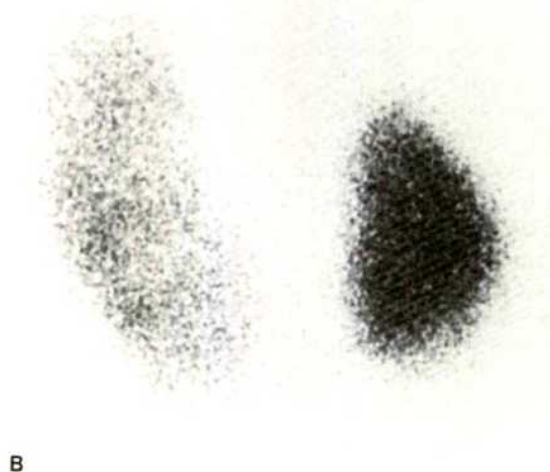
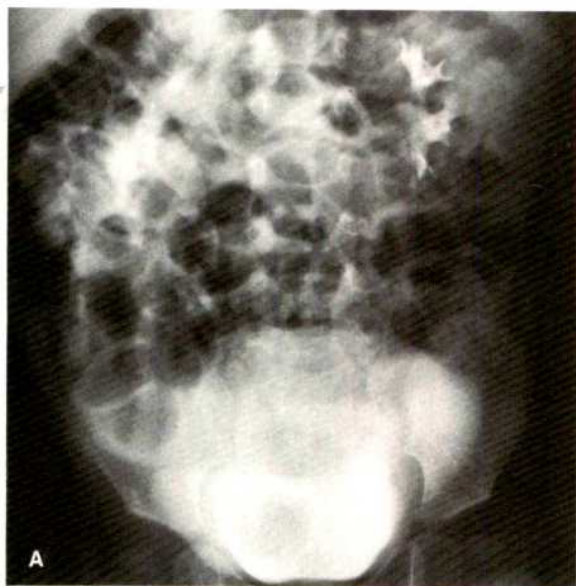


Fig. 1 Female aged 3 months: right duplex-system ectopic ureterocele. (A) The right upper renal pole is non-functioning on IVU. (B) ^{99m}Tc -DMSA scintigraphy shows the right lower pole to be functionally and anatomically normal.

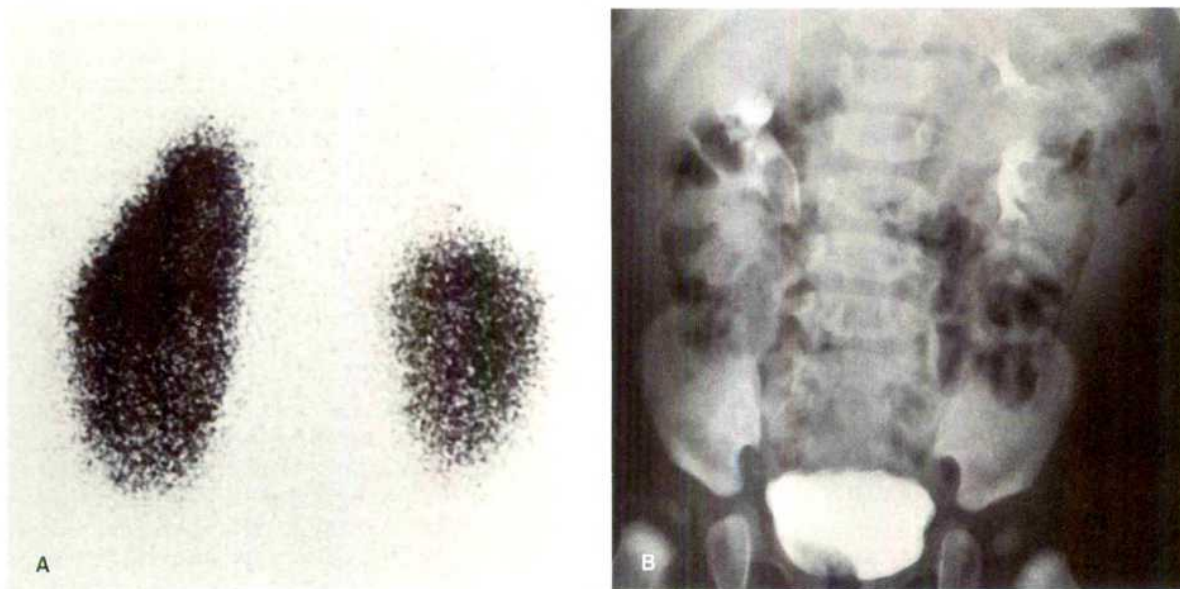


Fig. 2 Female aged 3 months: right intravesical duplex-system ureterocele. (A) IVU shows gross hydronephrosis of both renal poles. (B) ^{99m}Tc -DMSA scintigraphy shows that the uptake of isotope is generally reduced (38% of total) but is equally distributed to both renal poles. Right renal function returned to normal after excision of the ureterocele with bipolar ureteric reimplantation.

there was also contralateral VUR. One patient had pelviureteric junction obstruction in the lower polar system and 3 had non-refluxing dilatation of the lower polar ureter due to secondary obstruction by the ureterocele (2 ectopic, 1 orthotopic). Function of the lower renal pole was normal except in 2 cases where negligible function was associated with Grade III VUR.

Only 4 patients had clinical or radiological evidence of bladder outflow obstruction, of whom only 1 had global dilatation of the upper renal tracts. Lastly, one girl had calculi lying within the ureterocele.

Management

General policy. As a rule, where upper polar function was severely compromised, initial treatment comprised upper polar nephrectomy with aspiration of the ureterocele via the distal ureteric remnant, which was then left open with drainage post-operatively. Where there was useful function in the upper pole, but gross dilatation of its ureter, pyelopyelostomy was performed, again with aspiration of the ureterocele. In both groups antibiotic prophylaxis was given if VUR was not demonstrated post-operatively. Where good upper polar function was not associated with gross dilatation of the associated ureter, the ureterocele was excised and the ureters reimplanted within their common

sheath, if necessary with tailoring of the distal upper polar ureter. Some asymptomatic cases were managed expectantly when there was no evidence of bladder outflow obstruction and where the upper urinary tracts were otherwise normal, apart from the non-functioning upper renal pole and its associated ureter.

Upper polar nephrectomy. Twenty-three patients (3 with bilateral lesions) were initially treated by this means at ages ranging from 10 days to 4.7 years; 21 had truly ectopic and 2 had intravesical orthotopic lesions. There was 1 complication related to the procedure; nephropexy had not been performed, as was normally routine, and downward displacement of the hemi-kidney led to secondary pelviureteric junction obstruction requiring pyelolysis. Histological examination of the excised upper renal poles showed the appearance of severe dysplasia sometimes compounded by secondary inflammatory changes.

Post-operative cystography showed no VUR in 9 cases (3 Grade I, 4 Grade II, 2 Grade III) and contralateral VUR in 1.

Two children, both with truly ectopic lesions, later required excision of the ureterocele plus lower polar ureteric reimplantation, because of symptomatic breakthrough urinary infections associated with persisting VUR but not secondary renal

scarring. These procedures presented no difficulties and had a satisfactory outcome.

Twenty-one children (91%) in this treatment group have thus far required no further surgery during follow-up ranging from 0.5 to 6.2 years (mean 2). None has evidence of bladder outflow obstruction or obstructive changes in the lower polar ureter and at their most recent assessment 17 have no VUR and 4 have minor degrees of ipsilateral VUR.

Pyelopyelostomy. Three children, all with intravesical lesions, were treated by this means. One had ipsilateral lower polar pelviureteric junction obstruction and pyeloplasty was performed as part of the procedure. Two have good results, with diminution of upper polar dilatation and no VUR. In the other, dilatation remains unchanged, as does function. In this case the distal ureter had been ligated. Pyoureter developed some months later and was treated by excision of the ureterocele and its associated ureteric remnant plus lower polar ureteric reimplantation.

Primary excision of ureterocele. Five patients with intravesical lesions underwent this procedure together with bipolar ureteric reimplantation. Tailoring of the distal upper polar ureter was necessary on 1 occasion. All results were satisfactory, with improvement or resolution of dilatation and elimination of VUR.

Other surgical strategies. Two infants had virtual non-function of both renal poles. One, with unilateral disease, underwent nephroureterectomy plus excision of the (truly ectopic) ureterocele. The other had bilateral disease with, contralaterally, a non-functioning upper pole and a normally functioning lower pole with non-refluxing dilatation of its associated ureter. The non-functioning kidney with its associated ureters and ureterocele was excised together with contralateral upper polar nephrectomy. The lower polar ureteric dilatation resolved post-operatively. Nephrectomy specimens showed the appearance of severe congenital dysplasia in both renal poles.

Another infant, diagnosed prenatally, had a contralateral duplex-system anomaly with a urethrally ectopic ureter and lower polar VUR with renal rupture and pseudocyst formation. The complications and management of this patient are described elsewhere (Williams *et al.*, in preparation).

Expectant management. Eight patients satisfied our criteria for expectant management. Five had been diagnosed prenatally, while 3 girls presented with symptoms of cystitis which, it was felt, were unlikely to relate to the ureterocele. During follow-up, which ranged from 0.5 to 6 years (mean 2.3), none has had symptoms and serial ultrasound examinations remain unchanged from the presenting appearances.

Discussion

Despite the variable nature of duplex-system ureteroceles—and their secondary features—certain themes emerge from this series. Bladder outflow obstruction is uncommon and consequent secondary changes in the upper renal tracts are rarer still. Function of the upper renal pole is either virtually normal or virtually absent and in this series the former was always associated with ureteroceles which lay wholly intravesically and the latter with truly ectopic lesions. This observation accords with the contention of Mackie and Stephens (1975) that the severity of congenital polar dysplasia relates to the degree of any associated ureteric ectopia; with ureteroceles situated wholly intravesically this is minimal, so that good upper polar function would be anticipated. The virtual non-function found with truly ectopic ureteroceles is associated with histological appearances of severe congenital dysplasia and hence any surgical strategy intended to achieve useful functional recovery is unlikely to be rewarded. By contrast, lower polar function, if not always appearance, is usually perfectly preserved and exceptions to this rule are associated not with obstruction but rather with relatively severe VUR where there is again good reason to believe that the process represents congenital dysplasia rather than acquired reflux nephropathy. Lastly, limited experience of expectant management suggests that the natural history of duplex-system ureteroceles is somewhat more benign than hitherto supposed.

What are the implications for management? Clear indications for intervention are bladder outflow obstruction, with or without secondary changes in the upper renal tracts, obstruction of the lower polar ureter by the ureterocele and infection of the upper urinary tracts, especially if associated with VUR or with obstruction. Endoscopic ureterocele incision (Tank, 1980) has occasional value in an emergency but it is not usually regarded as definitive treatment. The difficulties of excising

ectopic ureteroceleles are well recognised and where the upper renal pole is virtually non-functioning, as is usually the case, its excision plus ureterocele aspiration represents a logical alternative. However, in some series (Mandell *et al.*, 1980; King *et al.*, 1983; Caldamone *et al.*, 1984), secondary excision of the ureterocele was necessary in 20 to 38% of patients, usually because of persisting VUR. In the present series the rate (9%) was much lower and VUR, if existing immediately post-operatively, tended to resolve in time. Although the collapsed ureterocele usually remained visible on ultrasonography, this appears to be inconsequential. In short, our experience thus far with this form of treatment has been satisfactory.

Where there is useful upper polar function, pyelopyelostomy has its advocates (Mandell *et al.*, 1980; King *et al.*, 1983; Decter *et al.*, 1989), yet this procedure is not without difficulty if it involves anastomosis of a massively dilated (and potentially infected) upper polar system to a lower polar renal pelvis of normal size. Good upper polar function is usually associated with wholly intravesical ureteroceleles which do not present the difficulties posed by truly ectopic lesions. Here we consider that the better policy is excision of the ureterocele plus bipolar reimplantation, if necessary with distal ureteric tailoring. In retrospect, our patients treated by pyelopyelostomy might have been better managed this way.

Lastly, what of expectant management? Our experience is too slight to advocate this policy and we merely draw attention to it as a possibility in appropriate circumstances. This might seem especially relevant in a proportion of asymptomatic infants diagnosed by prenatal ultrasonography.

References

- Caldamone, A. A., Snyder H. M. and Duckett, J. W. (1984). Ureteroceleles in children: follow-up of management with upper tract approach. *J. Urol.*, **131**, 1130–1132.
- Decter, R. M., Roth, D. R. and Gonzales, E. T. (1989). Individualised treatment of ureteroceleles. *J. Urol.*, **142**, 535–537.
- Gerridzen, R. and Schillinger, J. F. (1984). Transurethral puncture in management of ectopic ureteroceleles. *Urology*, **23**, 43–47.
- International Reflux Study Committee (1981). Medical versus surgical management of primary vesicoureteric reflux: a prospective international reflux study in children. *J. Urol.*, **125**, 277–283.
- Johnston, J. H. and Johnson, L. M. (1969). Experience with ectopic ureteroceleles. *Br. J. Urol.*, **41**, 61–70.
- King, L. R., Kozlowski, J. M. and Schacht, M. J. (1983). Ureteroceleles in children—a simplified and successful approach to management. *J. A.M.A.*, **249**, 1461–1465.
- Kroovand, L. R. and Perlmutter, A. D. (1979). A one-stage approach to ectopic ureterocele. *J. Urol.*, **122**, 367–369.
- Mackie, C. G. and Stephens, F. D. (1975). Duplex kidneys: a correlation of renal dysplasia with position of the ureteral orifice. *J. Urol.*, **114**, 274–277.
- Mandell, J., Colodny, A. H., Lebowitz, R. *et al.* (1980). Ureteroceleles in infants and children. *J. Urol.*, **123**, 921–926.
- Tank, E. S., Jr. (1980). Unroofing of ureteroceleles. Society for Pediatric Urology Newsletter, 30–31.
- Williams, D. I. and Woodard, J. R. (1965). Problems in the management of ectopic ureteroceleles. *J. Urol.*, **92**, 653–662.

The Authors

A. M. K. Rickwood, FRCS, Urological Surgeon.
I. Reiner, MD, Herbert Johnston Research Fellow.
M. Jones, FRCS, Surgical Registrar.
C. Pournaras, MD, Senior House Officer.

Requests for reprints to: A. M. K. Rickwood, Regional Department of Paediatric Urology, Royal Liverpool Children's Hospital (Alder Hey), Eaton Road, Liverpool L12 2AP.

Case Reports

Posterior Urethral Valves in Non-twin Siblings

P. A. BORZI, S. W. BEASLEY and R. FOWLER, *Department of General Surgery, Royal Children's Hospital, Melbourne, Australia*

Although the familial incidence of urinary anomalies such as vesicoureteric reflux and hypospadias is well documented, reports of non-twin siblings with posterior urethral valves are uncommon (Hasen and Song, 1955; Kjellberg *et al.*, 1957; Farkas and Skinner, 1976; Thomalla *et al.*, 1989). We describe 2 pairs of affected non-twin siblings, the fifth such report in the world literature.

Case Reports

Case 1. A 3-day-old male infant presented with lethargy, tachypnoea and a palpable left renal mass. Radiology demonstrated a poorly functioning left kidney, bilateral vesicoureteric reflux, a left perirenal urinoma and Type I posterior urethral valves. He underwent transurethral ablation of the valves and left nephroureterectomy.

Eight years later, at 3 weeks of age, his younger brother developed lethargy, vomiting and poor urinary stream. Following confirmation of Type I posterior urethral valves, he successfully underwent endoscopic valve ablation.

Case 2. At 38 weeks' gestation, a male infant was delivered in respiratory distress with dysmorphic features of "Potter's syndrome" and failed to survive. Autopsy revealed megacystis, bilateral megaureters, bilateral renal dysplasia and Type I posterior urethral valves.

Within 8 months his mother was again pregnant but serial prenatal ultrasound scans showed no urinary tract dilatation in the fetus. At 7 weeks of life this younger sibling presented with a poor urinary stream and a voiding cystourethrogram showed right vesicoureteric reflux and Type I posterior urethral valves. Endoscopic ablation of the valves was successful.

Comment

This report documents 2 pairs of non-twin siblings with posterior urethral valves. Familial and genetic studies of children with posterior urethral valves are suggestive of multifactorial determination (Reule and Ansell, 1967; Kroovand *et al.*, 1977; Michels *et al.*, 1981). The apparent increased

frequency of posterior urethral valves in siblings should encourage antenatal and postnatal screening to avoid delayed diagnosis and irreversible renal deterioration.

References

- Farkas, A. and Skinner, D. G. (1976). Posterior urethral valves in siblings. *Br. J. Urol.*, **48**, 76.
Hasen, H. B. and Song, Y. S. (1955). Congenital valvular obstruction of the posterior urethra in two brothers. *J. Pediatr.*, **47**, 207–215.
Kjellberg, S. R., Ericsson, N. O. and Rudhe, V. (1957). Urethral valves. In *The Lower Urinary Tract in Childhood. Some Correlated Clinical and Roentgenologic Observations*. Chapter 10, p. 203. Chicago: Yearbook Medical Publishers.
Kroovand, R. L., Weinberg, N. and Emami, A. (1977). Posterior urethral valves in identical twins. *Pediatrics*, **60**, 748.
Michels, V. V., Driscoll, D. J., Ledbetter, D. H. *et al.* (1981). Phenotype associated with ring 10 chromosome: Report of patient and review of literature. *Am. J. Med. Genet.*, **9**, 231–237.
Reule, G. R. and Ansell, J. S. (1967). Discordant occurrence of genitourinary defects in monozygotic twins. *J. Urol.*, **97**, 1078–1081.
Thomalla, J. V., Mitchell, M. E. and Garrett, R. A. (1989). Posterior urethral valves in siblings. *Urology*, **33**, 291–294.

Requests for reprints to: S. W. Beasley, Department of Surgery, Royal Children's Hospital, Flemington Road, Parkville, Victoria 3052, Australia.

Two Rare Genital Abnormalities: Crossed Testicular and Scroto-testicular Ectopia

H. DOĞRUYOL, M. ÖZCAN and E. BALKAN, *Departments of Paediatric and Plastic and Reconstructive Surgery, Uludağ University, Bursa, Turkey*

Cases of true testicular ectopia, excluding those in the superficial inguinal pouch, are rare (Murphy and Butler, 1985). In patients with crossed testicular ectopia, one testis deviates from the normal pathway of descent towards the contralateral scrotum and both testes are found on the same side. It is an extremely rare but well recognised condition (Beasley and Auldiss, 1985).

Cases of limited congenital scrotal anomalies have been reported. These include bifid scrotum, penoscrotal transposition, accessory scrotum and ectopic scrotum. Among these, ectopic scrotum is very rarely seen (Lamm and Kaplan, 1977). We

present 2 patients with genital anomalies and discuss their clinical characteristics and treatment.

Case Reports

Case 1. R.S., 137634-B, an 18-month-old boy, presented with a mass in the right inguinal area which had been noticed after birth. Physical examination revealed a right inguinal hernia. No testis was palpated on the left side. The child was admitted for a right herniotomy.

At operation 2 testes were found within the hernial sac; their appearance was good and they were identical in size (Fig. 1). Each had its own ductus and vascular pedicle derived from the appropriate side. To rule out polyorchidism the left inguinal canal and retroperitoneal space were also inspected via an extended right inguinal to suprapubic incision on the left side but no testis, spermatic vessels or ductus were found. Each testis was fixed in each hemiscrotum by translocation of the left testis from the right to the left side via the left inguinal canal. Convalescence was uneventful and the patient was normal 2 years post-operatively.

Case 2. S.A., 198401-Y, a 4-year-old boy, was admitted with a mass in the right inguinal area. On examination an ectopic right scrotal sac containing a palpably normal testis was found. The left hemiscrotum was well developed with a descended testis but without scrotal raphe. The penis was normal in appearance and location (Fig. 2). A right inguinal incision with a stitch sinus was detected.

This patient was the first child of a 21-year-old woman and vaginal delivery had been normal. There was no family history of congenital anomalies and no drugs of any kind had been taken during the first trimester of pregnancy. The child had had a right herniotomy at the age of 2 months.

Ultrasound demonstrated absence of the right kidney. This was confirmed by a ^{99m}Tc scan.



Fig. 1 Two testes of identical size within the hernia sac. Each testis has its own cord.

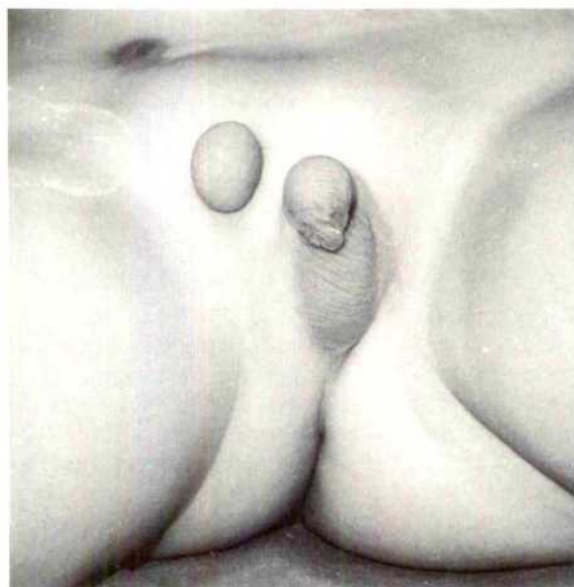


Fig. 2 Ectopic right inguinal scrotum containing palpably normal testis without scrotal raphe.

At operation the right ectopic hemiscrotum with testis was rotated to a normal position and sutured to the medial border of the normal scrotum. The post-operative course was uneventful.

Comment

The characteristic features of the true crossed ectopic testis have been described as follows.

1. Two testes are found on one side with no testis on the other side.
2. The 2 testes are identical in size and appearance.
3. Each testis has its own epididymis, ductus deferens and testicular vessels.
4. The vascular supply is derived from the appropriate side.
5. There is an associated hernia on the side of the 2 testes and no hernia on the contralateral side (Beasley and Auld, 1985).

According to this definition of the condition, only 30 cases have been accepted as authentic in the world literature up to 1983 (Doraiswamy, 1983). Including our patients, 9 new cases have been reported since then (Beasley and Auld, 1985; Miura and Takahashi, 1985; Pavão *et al.*, 1984; Tadera *et al.*, 1985; Vianna *et al.*, 1985; Gornall and Pender, 1987; Peters and Sing, 1987; Mouli *et al.*, 1988). Nevertheless, Tadera *et al.* (1985) stated that 66 cases of ectopia testis transversa had been

reported in the Japanese literature since 1912. In about 20% of such cases there is an association with persistence of müllerian structures (Gauderer *et al.*, 1982; Mouli *et al.*, 1988). Some authors are reluctant to include these patients with simple crossed testicular ectopia (Doraiswamy, 1983; Beasley and Auld, 1985).

Several procedures have been described for the treatment of the condition, including staged procedures and a modified Ombredanne operation (Pavão *et al.*, 1984). Contralateral laparotomy to differentiate between duplication of the testes and crossed ectopia have been suggested (Pavão *et al.*, 1984; Miura and Takahashi, 1985).

Routine biopsy of the ectopic testes has been advised because of a higher incidence of malignancy (Fujita, 1980; Pavão *et al.*, 1984), but in the absence of müllerian remnants there is little justification for this approach (Beasley and Auld, 1985).

The scrotum is regarded as relatively resistant to embryological misadventure (Lamm and Kaplan, 1977). Bifid scrotum is usually associated with intersex problems, but penoscrotal transposition is unrelated to them. Accessory scrotum is classified as mid-perineum and lateral perineum types (Yokokawa *et al.*, 1988). The mid-perineum type is accepted as a teratoid structure (Takayasu *et al.*, 1974).

Three types of scrotal ectopia have been described, including unilateral penoscrotal transposition with or without scrotal raphe and abnormal migration of the inferior division (Lamm and Kaplan, 1977). Penoscrotal transposition without scrotal raphe is due to defective migration of labioscrotal swelling (Lamm and Kaplan, 1977).

Most of these malformations are associated with other urogenital anomalies. These include bifid scrotum, hypospadias, chordee, absent scrotal raphe and renal agenesis (Kolandaivelu *et al.*, 1987). Renal agenesis is always on the same side as the ectopic scrotum, as in our case.

The ectopic scrotum occasionally contains testes (Milroy, 1969). In this case, the testis in the ectopic scrotum can also be accepted as ectopic.

Surgical correction of the ectopic scrotum is done by rotating and suturing it to the normal hemiscrotum with the testis.

References

- Beasley, S. W. and Auld, A. W. (1985). Crossed testicular ectopia in association with double incomplete testicular descent *Aust N.Z J Surg.*, **55**, 301-303.

- Doraiswamy, N. V. (1983). Crossed ectopic testis. Case report and review. *Z. Kinder Chir.*, **38**, 264-268.
- Fujita, J. (1980). Transverse testicular ectopia. *Urology*, **16**, 400-402.
- Gornall, P. G. and Pender, D. J. (1987). Crossed testicular ectopia detected by laparoscopy. *Br J Urol.*, **59**, 283.
- Kolandaivelu, G., Seendraj, K., Bose, J. C. *et al.* (1987). Accessory scrotum. *Br J Urol.*, **59**, 363.
- Lamm, D. L. and Kaplan, G. W. (1977). Accessory and ectopic scrota. *Urology*, **9**, 149-153.
- Milroy, E. (1969). Ectopic scrotum. A review of the literature and report of a further case. *Br J Urol.*, **41**, 235.
- Miura, T. and Takahashi, G. (1985). Crossed ectopic testis with common vas deferens. *J. Urol.*, **134**, 1206-1208.
- Mouli, K., McCarthy, P., Ray, P. *et al.* (1988). Persistent müllerian duct syndrome in a man with transverse testicular ectopia. *J. Urol.*, **139**, 373-375.
- Murphy, D. M. and Butler, M. R. (1985). Preperitoneal ectopic testis: a case report. *J. Pediatr Surg.*, **20**, 93-94.
- Pavão, J. M., Gonzaga, R. A. F., Cardoso, J. A. G. *et al.* (1984). Transverse testicular ectopia corrected by a modified Ombredanne operation. *J. Urol.*, **132**, 1194.
- Peters, J. H. and Sling, S. (1987). Transverse testicular ectopia: a case report. *Del. Med. J.*, **59**, 333-335.
- Tadera, S., Der, S., Kamidono, S. *et al.* (1985). A case of ectopia testis transversa. *Hinyokika Kyo*, **31**, 701-704.
- Takayasu, H., Ueno, A. and Tanaka, O. (1974). Accessory scrotum, a case report. *J. Urol.*, **135**, 593-594.
- Vizama, R. S., de Freitas-Filho, Z. G., Moura, D. V. *et al.* (1985). Crossed testicular ectopia associated with bilateral cryptorchidism. *Rev. Paul. Med.*, **103**, 215.

Requests for reprints to: H. Doğruyol, Uludağ Üniversitesi, Tıp Fakültesi, Çocuk cerrahisi Anabilim Dalı, Duşınar, Bursa, Turkey.

Regression of Lymphadenopathy in Patient with Prostatic Carcinoma after Hormonal Manipulation

C. CONSTANTINIDES, G. ALIVIZATOS, D. MITROPOULOS and C. DIMOPOULOS, *Department of Urology, Laiko Hospital, Athens, Greece*

Case Report

A 73-year-old man presented with an 11-month history of dysuria, urgency and haematuria. Digital examination of the prostate gland revealed the possibility of carcinoma. Transrectal needle biopsy confirmed prostatic carcinoma with a Gleason score of 4. The chest X-ray was clear and intravenous urography demonstrated a normal upper

urinary tract. The bone scan was negative but CT scan of the abdomen revealed gross enlargement of the retroperitoneal lymph nodes (Fig. 1). PSA was 19.1 ng/ml and flow cytometric analysis of the biopsy tissue revealed diploid tumour cells.

For this T3N3MO tumour we performed a transurethral resection of the prostate in order to overcome the obstruction. Histological examination confirmed the initial diagnosis and a Gleason score of 5 was ascribed.

The patient was given an LHRH analogue and cyproterone acetate. When assessed 6 months later he had no symptoms of bladder outlet obstruction. PSA was 5.4 ng/ml and the bone scan remained negative. CT scan of the abdomen showed dramatic regression of the enlarged retroperitoneal lymph nodes (Fig. 2).

Comment

This response to hormonal manipulation is rarely found in patients with prostatic carcinoma who have massive nodal involvement and negative bone scans. The relationship of grade and extent of local tumour to pelvic node involvement has been studied

by Zincke *et al.* (1982) and Smith *et al.* (1983). It has also been reported that prostatic carcinoma with a Gleason score of 4 or 5 may be a heterogeneous group in terms of biological malignant potential (McNeal *et al.*, 1986). Sandhu *et al.* (1990) stated that the survival rate of patients with lymphadenopathy but negative bone scans at diagnosis was significantly better than that of patients with both node and bone disease. The suggestion that vigorous treatment should be applied to all patients with advanced lymph node disease (Sandhu *et al.*, 1990) is supported by the outcome in our patient.

References

- McNeal, J. E., Kindrachuk, R. A., Frei, F. S. *et al.* (1986). Patterns of progression in prostate cancer. *Lancet*, **1**, 60–63.
- Sandhu, D. P. S., Mayor, P. E., Sambrook, P. *et al.* (1990). Increased survival of patients with massive lymphadenopathy and prostate cancer. Evidence of heterogeneous tumour behaviour. *Br. J. Urol.*, **66**, 415–419.
- Smith, J. A., Seaman, J. P., Gleidman, J. B. *et al.* (1983). Pelvic lymph node metastasis from prostatic cancer: influence of tumor grade and stage in 452 consecutive patients. *J. Urol.*, **130**, 290–292.
- Zincke, H., Farrow, G. M., Myers, R. P. *et al.* (1982). Relationship between grade and stage of adenocarcinoma of the prostate and regional lymph node metastases. *J. Urol.*, **128**, 498–501.

Requests for reprints to: C. Constantinides, Laiko Hospital, Department of Urology, 17, Ag. Thoma Str., GR-115 27 Athens, Greece.



Fig. 1 Gross enlargement of retroperitoneal lymph nodes.



Fig. 2 Regression of lymph nodes 6 months after hormonal treatment.

Right-sided Varicocele Caused by False Aneurysm from Aortic Graft

M. P. CORLETT, B. R. GWYNN and J. D. HAMER,
Department of Surgery, Queen Elizabeth Hospital,
Birmingham

Case Report

A 68-year-old doctor who had 6 years previously undergone abdominal aortic aneurysm repair presented with a 3-week history of right loin pain radiating to the right testis. A right-sided varicocele had developed 6 months before admission.

There was right-sided abdominal tenderness but no palpable masses. A large right-sided varicocele was present.

Intravenous urography, a midstream specimen of urine, ultrasound and intravenous digital subtraction angiography were unhelpful, but abdominal CT scan revealed "a para-aortic mass to the right of the midline involving the psoas muscle extending from above the level of the renal arteries to below the aortic bifurcation" (Fig.).



Fig. Abdominal CT scan showing para-aortic mass obscuring the outline of the aorta and graft.

Laparotomy revealed a pulsatile retroperitoneal mass extending across the right renal vein, anterior to the inferior vena cava, which proved to be a false aneurysm arising from a disrupted proximal aortic anastomosis. After graft replacement the patient's post-operative recovery was uneventful. The varicocele rapidly diminished in size.

Comment

Right-sided varicoceles are rare because the right testicular veins drain directly into the inferior vena cava. The development of varicoceles due to obstruction of the left testicular veins by a tongue of renal adenocarcinoma is well recognised (Clain, 1980). Similarly, varicoceles may occur secondary to retroperitoneal tumours (Saha, 1977).

Aneurysm rupture into the left renal vein causing left-sided varicocele has been described (Linsell *et al.*, 1987), but in this case compression of the right testicular veins by an expanding false aneurysm was the likely cause of the varicocele, and this is previously unreported.

The sudden onset of varicocele on either side should raise suspicion and careful retroperitoneal imaging is required.

References

- Clain, A. (ed.) (1980). *Hamilton Bailey's Demonstration of Physical Signs in Clinical Surgery*. Sixteenth edition. Chapter 25, p. 370. Bristol: Wright.
- Linsell, J. C., Rowe, P. H. and Owen, W. J. (1987). Rupture of an aortic aneurysm into the renal vein presenting as a left sided varicocele. *Acta Chir. Scand.*, **153**, 477-478.
- Saha, S. K. (1977). Retroperitoneal liposarcoma. *Br. J. Urol.*, **49**, 92.

Requests for reprints to: M. P. Corlett, Department of General Surgery, Walsgrave Hospital, Clifford Bridge Road, Coventry CV2 2DX.

Primary Actinomycosis of the Urinary Bladder

A. P. MAKAR, J.-P. MICHIELSEN, G. J. BOECKX and E. A. VAN MARCK, *Departments of Gynaecology, Urology and Pathology, St Camillus University Hospital, Antwerp, Belgium*

Primary actinomycosis of the bladder is very rare. Only 7 cases have been reported since 1922.

Case Report

A 35-year-old woman was hospitalised because of incapacitating lower abdominal pain and urgency. Her previous history showed 2 normal labours. A copper-containing intrauterine device had been placed after her second labour in 1984. Since 1987 she had complained of lower abdominal pain, urgency and dysuria. Multiple short courses of antibiotics (trimethoprim, norfloxacin) were prescribed with temporary improvement. Urine cultures failed to reveal pathogenic organisms. Blood examination on admission showed leukocytosis $12,200 \text{ wbc}/\text{m}^3$ with 83% polymorphonuclear leukocytes, sedimentation rate 20/42. Intravenous urography showed a filling defect in the bladder roof. Transvesical ultrasonography showed complete infiltration of the bladder roof and the perivesical tissues by tumour. Cystoscopy showed ventral vegetative proliferations and biopsy showed an aspecific chronic inflammatory reaction and fibrosis. Endometrial curettage revealed non-specific endometritis on microscopic examination.

CT scan of the abdomen showed tumour in the upper wall of the bladder with infiltration into the rectus abdominis muscle (Fig. 1). Laparotomy revealed a bladder mass adherent to the pubis and omentum. Partial cystectomy was performed and a bladder fragment containing central exophytic tumour $4 \times 4.2 \times 3.5 \text{ cm}$ was removed. Histological examination, using haematoxylin-eosin, Gram (Brown and Brenn) (Fig. 2), PAS and Ziehl-Neelsen stains, revealed an inflammatory pseudo-tumour



Fig. 1 CT scan showing infiltration of tumour (bar) into the upper part of the bladder, perivesical area and rectus abdominis. The tumour has an hour-glass appearance.

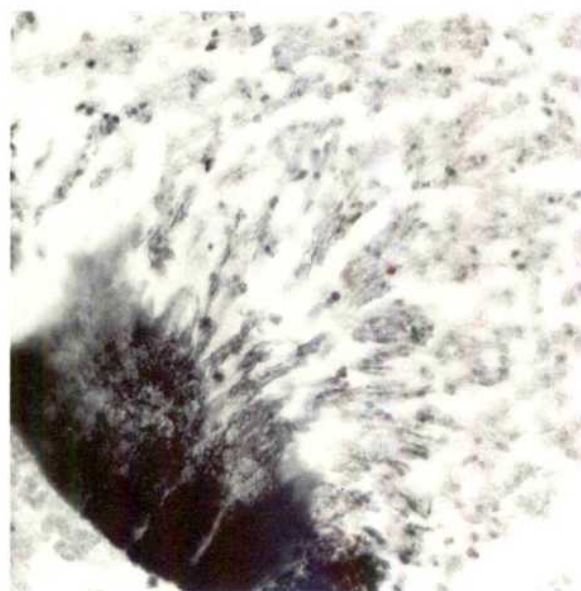


Fig. 2 Gram stain reveals Gram-positive filaments within the grain (Brown and Brenn Gram stain $\times 400$).

with micro-abscesses containing Gram-positive, non-acid-fast actinomycotic grains. The patient received penicillin as follows: 20 million units/day intravenously for 2 weeks, then 6 million units/day intramuscularly for 4 weeks followed by ampicillin 1500 mg/day orally for a total period of 4 months. Follow-up 16 months later showed no evidence of relapse.

Comment

Actinomycosis of the bladder presents as lower abdominal pain, urgency and recurrent cystitis. Trauma and intrauterine devices may contribute to

the infection (King and Lam, 1978; Villani *et al.*, 1987).

There is usually a long interval between the onset of symptoms and establishment of the diagnosis. In our case it was 30 months.

The diagnosis is mainly histological. Actinomycosis should be considered in the differential diagnosis of every bladder mass (King and Lam, 1978; Villani *et al.*, 1987).

A combination of surgery and long-term antibiotic therapy remains a successful policy. Penicillin is the drug of choice (Jackson *et al.*, 1988).

References

- Jackson, A. E., Parry, J. R. W. and Shah, P. J. R. (1988). Ureteric obstruction secondary to pelvic actinomycosis. *Br. J. Urol.*, **62**, 85–87.
- King, D. T. and Lam, M. (1978). Actinomycosis of the urinary bladder and association with an IUD. *J.A.M.A.*, **240**, 1512–1516.
- Villani, U., Leoni, S., Pastorello, M. *et al.* (1987). Actinomycosis of the bladder and intrauterine devices. *Br. J. Urol.*, **60**, 463–464.

Requests for reprints to: A. P. Makar, Department of Gynaecological Oncology, Norwegian Radium Hospital, Montebello 0330, Oslo 3, Norway.

Extraskelatal Ewing's Sarcoma Metastatic to Penis

J. JIMÉNEZ-VERDEJO, P. L. FERNÁNDEZ, A. HADDAD, A. GARCIA-CARRIAZO, A. ZULUAGA and F. NOGALES, Departments of Urology, Pathology and Radiology, University Hospital, Granada, Spain

Metastases to the penis are infrequent, although more than 200 cases have been reported in the literature. We present a case of metastatic Ewing's sarcoma in this site.

Case Report

A 22-year-old man with a previous diagnosis of extra-skeletal Ewing's sarcoma in the right pelvic cavity treated with excision, radiotherapy and chemotherapy (ACT-D, VCR, CTX and ADM), presented 18 months later with an exrescent and ulcerative lesion on the glans and foreskin (Fig. 1). Biopsy showed a neoplasm composed of solid nests of small basophilic cells in the dermis which compressed the epidermis (Fig. 2). Nuclei were monotonous, round to oval, with more than 30 mitoses/10 hpf and scant clear cytoplasm. PAS stain showed PAS-



Fig. 1 Excrescent and ulcerative lesion on glans penis and foreskin.

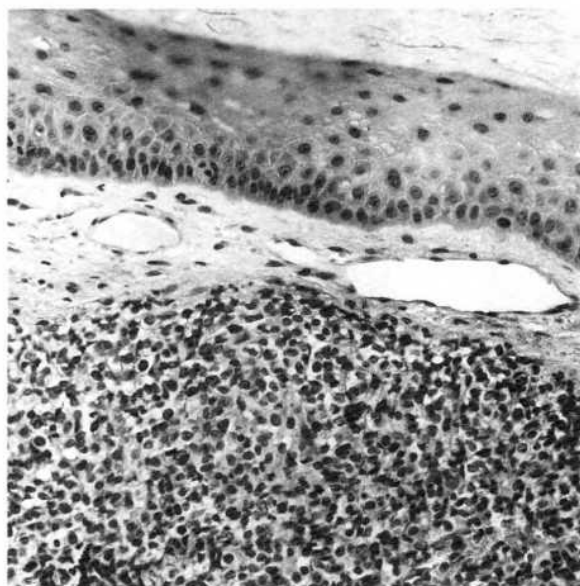


Fig. 2 Neoplasm composed of small basophilic cells in the dermis. (H and E $\times 100$).

positive globules in many cells. Immunoperoxidase stains for neuron-specific enolase, common leucocytic antigen and vimentin yielded positive results only for the latter. Electron microscopy showed glycogen vacuoles within tumour cells. The patient underwent amputation and chemotherapy and died some months later.

Comment

Although many cases of metastases to the penis have been reported (Abeshouse and Abeshouse, 1961; Powell *et al.*, 1985), this is, to our knowledge, the first case in which an extraskeletal Ewing's sarcoma is the origin. The primary sites are usually in the genitourinary tract and gastrointestinal area. In the present case, the origin in the previous neoplasm was confirmed by immunohistochemistry and electron microscopy, which eliminated other small cell neoplasms such as lymphoma and neurogenic tumours (Wick, 1989), although the exact nature of Ewing's sarcoma has not yet been established.

References

- Abeshouse, B. S. and Abeshouse, G. A. (1961). Metastatic tumors of the penis: a review of the literature and a report of two cases. *J. Urol.*, **86**, 99–112.
- Powell, B. L., Craig, J. B. and Muss, H. B. (1985). Secondary malignancies of the penis and epididymis. A case report and review of the literature. *J. Clin. Oncol.*, **3**, 110–116.
- Wick, M. R. (1989). Immunohistochemistry in the diagnosis of "solid" malignant tumors. In *Immunohistology in Diagnostic Pathology*, ed. Jennette, J. C. Chapter 5, pp. 161–192. Boca Raton: CRC Press.

Requests for reprints to: P. L. Fernández, Departamento de Anatomía Patológica, Facultad de Medicina, 18012 Granada, Spain.

Haematuria after Exercise following Pelvic Fracture

L. JONES and R. C. L. FENELEY, *Department of Urology, Southmead Hospital, Bristol*

Case Report

A 16-year-old boy fell under a horse and sustained a butterfly fracture of the pelvis which was treated conservatively. He experienced no problems passing urine and urine analysis was negative. Six months after the injury painless haematuria occurred on the first void after a strenuous run. After this episode the pattern was repeated whenever he indulged in sporting activities.

Physical examination was normal. Microscopy of urine during periods of rest showed 2–4 rbc/hpf only.

Intravenous urography showed normal upper tracts; lower tract films demonstrated a fine spicule of bone protruding from the healing fracture of the superior pubic ramus (Fig.).



Fig.

Cystoscopy revealed a 0.75 cm diameter stone fixed to the anterior wall of the bladder. Litholapaxy was performed, exposing a spicule of bone penetrating the anterior bladder wall. The bladder was opened via a suprapubic approach and the spicule was chiselled from the right pubic ramus. Analysis of the stone showed it to be composed of calcium oxalate. Three months following the operation there was no recurrence of haematuria.

Comment

Haematuria following strenuous exercise has been well documented and occurs in 25% of runners following a marathon; reviews of haematuria following exercise agree that abnormalities resolve over 24 to 48 h and that a clinical examination and urine analysis taken during a period of rest are required for investigation (Kincaid-Smith, 1982; Reid *et al.*, 1987).

A bladder stone causing frank painless haematuria after exercise has been previously reported (Thomas, 1985), but this was not associated with trauma or fracture. Minimal abnormalities at urine analysis during periods of rest were common to both cases.

References

- Kincaid-Smith, P. (1982). Haematuria and exercise-related haematuria. *Br. Med. J.*, **285**, 1595-1597.
 Reid, R. I., Hosking, D. H. and Ramsey, E. W. (1987). Haematuria following a marathon run: source and significance. *Br. J. Urol.*, **59**, 133-136.

Thomas, P. L. (1985). Haematuria, running, bladder stone. *Br. J. Sports Med.*, **19**, 49.

Requests for reprints to: R. C. L. Feneley, Department of Urology, Southmead Hospital, Westbury-on-Trym, Bristol BS10 5NB.

Laparoscopic Removal of Intra-abdominal Testis

L. H. STEWART, R. N. HEASLEY and W. G. G. LOUGHRIDGE, *Departments of Urology, and Obstetrics and Gynaecology, Belfast City Hospital, Belfast*

The laparoscope is employed increasingly outside the field of gynaecology. Gibson *et al.* (1990) reported its use in this centre to reposition blocked continuous ambulatory peritoneal dialysis (CAPD) cannulae, and we now describe what we believe to be the first endoscopic removal of an intra-abdominal testis.

Case Report

An 18-year-old man presented with a non-palpable right testis. Clinically no testis was found either in the scrotum or along the inguinal canal. An ultrasound scan failed to identify its position and an intravenous urogram was normal. The increased risk of malignancy in an intra-abdominal testis makes it essential to identify and, if present, remove it.

Rather than subject the patient to further imaging techniques or proceed directly to laparotomy, we resorted to laparoscopy which clearly identified the testis lying at the internal ring (Fig.). The testis was seen to be mobile, being held only by the gubernaculum, so that endoscopic removal appeared feasible.

With 2 further manipulators inserted by stab incisions into the right iliac fossa, 2 Filshie clips were placed across the testicular vessels and one across the gubernaculum. These structures were then divided with endoscopic scissors and the freed testis grasped and removed through the larger of the 2 stab incisions without need to enlarge it. The patient made an uneventful recovery and was discharged home 4 days later.

Comment

The role of laparoscopy has been widening for many years, especially in general surgery, where both laparoscopic appendicectomy (Leahy, 1989) and cholecystectomy (Reddick and Olsen, 1989) have been performed, but its use in urology has remained limited. Gibson *et al.* (1990) described

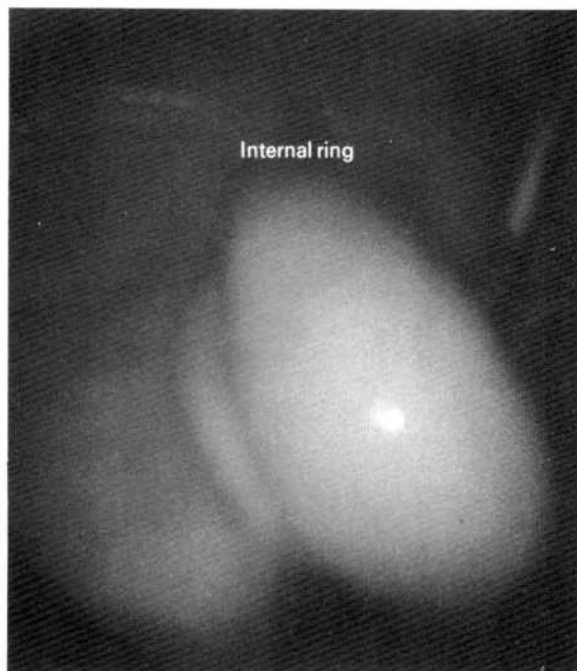


Fig. View through laparoscope showing the testis lying at the internal ring.

the use of the laparoscope to reposition blocked CAPD cannulae, and although the laparoscope has already been used to identify the position of intra-abdominal testes (Guiney *et al.* 1989), endoscopic removal has not been reported.

The technique described was simple for a trained laparoscopist and there was minimal upset to the patient, who could have been discharged within 24 h had it not been for our desire to observe him closely following this new technique.

References

- Gibson, D. H., Heasley, R. N. Price, J. H. *et al.* (1990). Laparoscopic repositioning of blocked peritoneal dialysis catheters in patients on CAPD. *Clin. Nephrol.*, **33**, 208.
- Guiney, E. J., Corbally, M. and Malone, P. S. (1989). Laparoscopy and the management of the impalpable testis. *Br. J. Urol.*, **63**, 313–316.
- Leahy, P. F. (1989). Technique of laparoscopic appendicectomy. *Br. J. Surg.*, **76**, 616.
- Reddick, E. J. and Olsen, D. O. (1989). Laparoscopic laser cholecystectomy. A comparison with mini-lap cholecystectomy. *Surg. Endosc.*, **3**, 131–133.

Requests for reprints to: L. H. Stewart, Department of Urology, Belfast City Hospital, Lisburn Road, Belfast BT9 7AB.

Points of Technique

The Rat-tail Catheter in Ureteroneocystostomy Operations

K. ANAFARTA, T. YURDAKUL and Y. BEDUK, *Department of Urology, University of Ankara, Ankara, Turkey*

Ureteric stents are used in ureteroneocystostomy procedures to prevent ureteric kinking and oedema around the anastomosis, to facilitate wound healing and to prevent urinary leakage (Saltzman, 1988). Specially designed silicone tubes and feeding tubes have been used for this purpose but in recent years double-pigtail ureteric catheters have been preferred (Finney, 1982).

When these methods are used, urinary drainage is assisted by a urethral catheter. We have used the rat-tail catheter (Rüsch, Waiblingen, Germany), which is mainly employed in ureteropyeloplasty procedures (Fig. 1A) as both a ureteric stent and a urethral catheter in ureteroneocystostomy operations.

Technique

The rat-tail catheter with balloon has been used in 10 patients with primary obstructed megaureter and vesicoureteric reflux who underwent unilateral ureteroneocystostomy using intravesical methods.

The balloon of the rat-tail catheter was inserted urethrally, inflated and fixed at the neck of the bladder with the ureteric part placed in the ureter as a stent, following completion of the anastomosis (Fig. 1B). No incompatibility was observed between the calibration of the urethral and ureteric sections.

Comment

When used as a urethral catheter and a ureteric stent the rat-tail catheter is easy to insert and there is no need for a second procedure to remove the stent.

No difference was found in the post-operative infection rate following the use of rat-tail catheters and other stents.

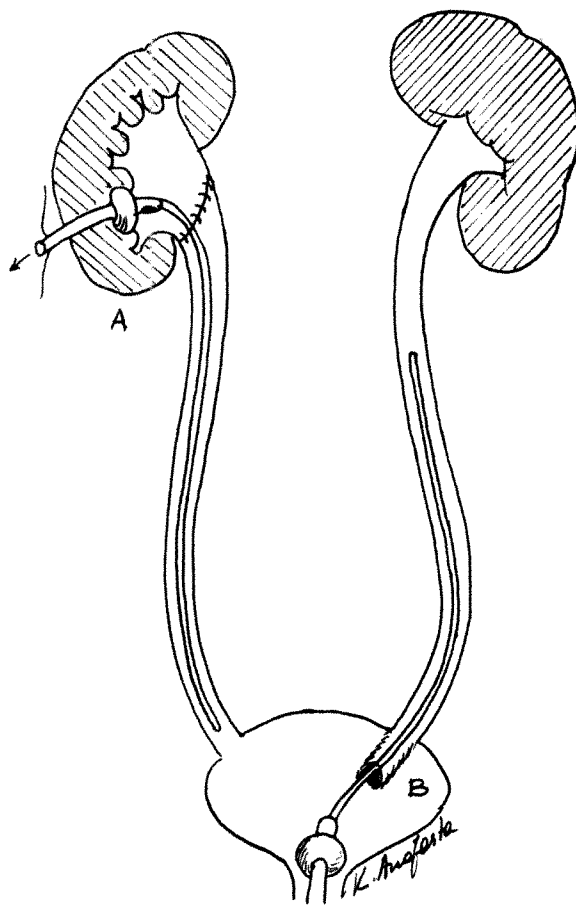


Fig. 1 (A) Conventional use of rat-tail catheter in pyeloplasty procedure. (B) Rat-tail catheter used in neocystostomy procedure.

This method is not felt suitable for patients with long-term indwelling stents but for short-term use and in ureteroneocystostomy procedures the rat-tail catheter is preferable to other ureteric stents.

References

- Finney, R. P. (1982). Double-J and diversion stents. *Urol. Clin. North Am.*, **9**, 89–94.
- Saltzman, B. (1988). Ureteral stents. Indications, variations, and complications. *Urol. Clin. North Am.*, **15**, 481–491.

Requests for reprints to: K. Anafarta, Ankara Universitesi Tıp Fakultesi, Üroloji Anabilim Dalı İbn-i Sina Hastahanesi, Samanpazari, Ankara, Turkey.

The Autoinjector Device: An Aid to Intracavernosal Pharmacotherapy

H. W. GILBERT and J. C. GINGELL, *Department of Urology, Southmead Hospital, Westbury-on-Trym, Bristol*

Self-injection with intracavernosal vasoactive agents is an effective method of treating many men with impotence (Juenemann and Alken, 1990). Unfortunately, a significant number of patients are unable to inject themselves, even though a good response has been obtained, either because they are anxious or are frightened of needles (Althof *et al.*, 1989). Another cause of failure is obesity; the pendulous abdomen obscures the injection site. We report the use of a device which can circumvent these problems.

The Autoinjector (Owen Mumford, Oxon) is a spring-loaded gun which automatically administers the contents of a pre-loaded syringe and hypodermic needle. The device is fully adjustable to the individual needs of each patient. The effective dose of vasoactive agent is drawn up into either a 1 ml (U-100) or 2 ml (U-40) insulin syringe with integral needle (Becton Dickinson Co., Dublin, Eire) which is then loaded into the Autoinjector. The needle guard (Fig. 1) is placed over a pre-determined injection site, free of large veins, on the dorsolateral aspect of the base of the penis. The needle guard can be used by an obese patient to guide the needle to the correct site and by an anxious patient to steady the needle prior to injection (Fig. 2). The gun is then fired at the touch of a button.

Four men who had not been able to inject themselves because of their fear of needles are now using the device and are established on self-injection

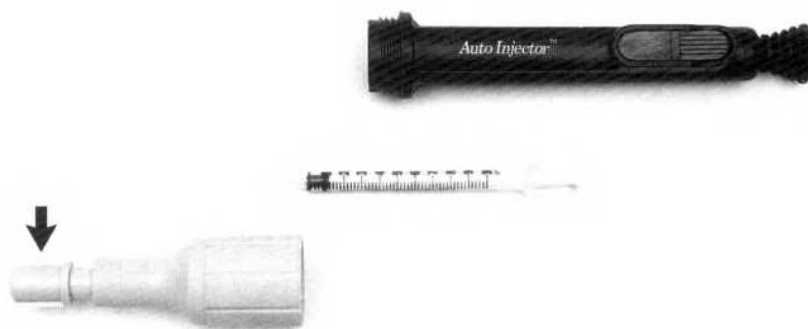


Fig. 1 The Autoinjector device (the needle guard is arrowed).



Fig. 2 The loaded device held in position prior to injection.

therapy. In addition, 2 obese men unable to see their penises have resumed sexual intercourse.

In conclusion, the Autoinjector device is a useful aid which allows some men who are unable to use intracavernosal pharmacotherapy to enjoy its benefits.

References

- Althof, S. E., Turner, L. A., Levind, S. B. *et al.* (1989). Why do so many people drop out from auto-injection therapy for impotence? *J. Sex. Marital. Ther.*, **15**, 121–129.
- Juenemann, K.-P. and Alken, P. (1990). Pharmacotherapy for erectile dysfunction; a review. *Int. J. Impotence Res.*, **1**, 71–93.

Requests for reprints to: H. W. Gilbert, Department of Urology, Southmead Hospital, Westbury-on-Trym, Bristol BS10 5NB.

Suprapubic Catheterisation and Bowel Injury

A. PARIKH, C. R. CHAPPLE and S. J. HAMPSON,
Department of Urology, Middlesex Hospital, London

Suprapubic catheterisation is a recognised technique for urinary drainage in situations where bladder catheterisation is indicated and where a functional assessment of voiding function is necessary. Many devices are available for the implementation of the procedure, most of which rely on trocar and cannula principles, either passing the catheter over a trocar (Argyle, Bonano, Stamey) or through a cannula (Nottingham). These procedures may be carried out under either general or local anaesthesia. Bowel damage is a possibility given the blind stabbing nature of the trocar-based devices and we report 2 such cases. In circumstances where the bladder cannot be adequately distended we have found that a technique using a Heygroves curved dilator is safer than a blind suprapubic stab insertion.

Case Reports

Case 1. An 82-year-old woman developed bladder outflow obstruction secondary to radiation cystitis; she had previously undergone pelvic surgery and radiotherapy. Subsequent detrusor failure and an inability to self-

catheterise necessitated a suprapubic catheter. A Foley catheter was inserted without difficulty under general anaesthesia. Nine months after the original insertion she was noted to have intestinal contents in the catheter bag. A cystogram through the catheter showed a fistula communicating with the small bowel (Fig. 1). A short segment of intestine was resected and the suprapubic catheter sited under direct vision. Her recovery was uneventful.

Case 2. A 92-year-old woman was referred for insertion of a suprapubic catheter to control intractable incontinence, a urethral catheter having been found unacceptable. She had had previous pelvic radiotherapy. A Foley catheter was inserted with the Nottingham introducer as above; 12 h later she was noted to be draining intestinal contents and to have local peritonism. A cystogram demonstrated a vesico-intestinal fistula (Fig. 2). At laparotomy the catheter was found to pass through the small bowel and a local resection was undertaken. Again the catheter was resited under direct vision.

Comment

Suprapubic catheterisation is an important technique in the management of patients and in most cases the presence of a large bladder allows an easy extraperitoneal puncture through the midline. However, patients with reduced bladder capacity cannot be distended and those who have undergone pelvic surgery or radiotherapy may have loops of

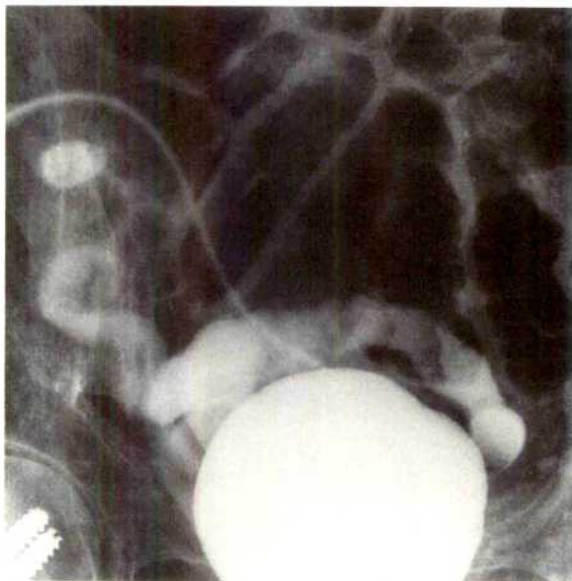


Fig. 1 Cystogram showing vesico-intestinal fistula.



Fig. 2 Vesico-intestinal fistula immediately following suprapubic catheterisation. There is bilateral reflux and marked urethral leakage; the latter contributed to difficulty in adequately distending the bladder.

intestine adherent to the bladder. We now use the Heygroves urethral sound for such patients. The technique is described in detail by Turner-Warwick (1988). In brief, a small suprapubic incision is extended down to the linea alba and the Heygroves urethral sound passed *per urethram* to a finger introduced into this incision. The sound is guided through the bladder wall and a catheter tied to the sound with a long loop of nylon. The catheter is pulled into the bladder and disconnected from the sound after confirming the catheter's position by bladder washout.

There appear to be no reports of small bowel injury following suprapubic catheterisation, although colonic injury has been reported (Morse *et al.*, 1988). The risk of intestinal injury during suprapubic catheterisation is minimised by using a Heygroves sound and therefore represents the technique of choice when any of the above hazards exist.

References

- Morse, R. M., Spirnak, J. P. and Resnick, M. I. (1988). Iatrogenic colon and rectal injuries associated with urological intervention; report of 14 patients. *J. Urol.*, **140**, 101–103.

Turner-Warwick, R. T. (1988). Urethral stricture surgery. In *Current Operative Surgery: Urology*, ed. Mundy, A. R. Chapter 12, pp. 166–168. London: Bailliere Tindall.

Requests for reprints to: S. J. Hampson, Department of Urology, Middlesex Hospital, Mortimer Street, London W1N 8AA.

Nephrostomy Tubes Resistant to Removal

L. H. STEWART, R. M. KERNOHAN and W. G. G. LOUGHRIDGE, *Department of Urology, Belfast City Hospital, Belfast*

Case Reports

Case 1. A 45-year-old man, lost to follow-up for 1 year after percutaneous nephrolithotomy, returned with his nephrostomy tube (Cook Surgical Malecot, Polyethylene, 16F) still *in situ*. On attempting removal an introducer was inserted to straighten the "wings" of the Malecot, but great difficulty was encountered in removing the tube, which eventually broke, leaving the "wings" behind. When the tract was inspected using a ureteroscope, the broken "wings" were easily seen but could not be removed because of a band of tissue growing through them. The patient's tract healed rapidly and he suffered no adverse effects in the subsequent 3 months.

Case 2. A 63-year-old man presented with a bladder tumour and non-functioning right kidney. His left kidney also became obstructed and a percutaneous nephrostomy tube (Cook Surgical Malecot, Polyethylene, 16F) was inserted to achieve drainage. Three months later, following radiotherapy to his bladder, an antegrade pyelogram showed adequate drainage and it was decided to remove the nephrostomy tube. After insertion of the introducer, difficulty was encountered in removing the tube, which broke, leaving the "wings" behind. The patient has suffered no adverse effects in the 2 months since attempted removal.

Comment

Complications arising from nephrostomy tubes are rare and usually relate to their insertion (Lee *et al.*, 1987). Fragmentation of long-term ureteric stents is not uncommon (Moskovitz *et al.*, 1989). However, we are not aware of fragmentation affecting percutaneous nephrostomy tubes. The reason for the resistance to removal and eventual breakage

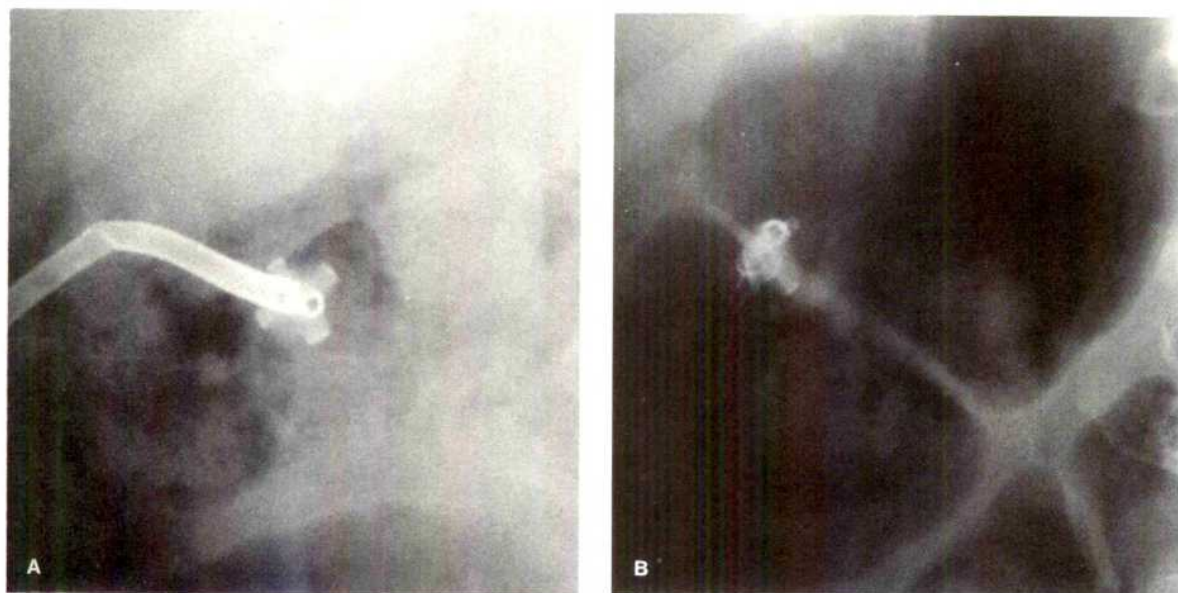


Fig. 1 X-ray in Case 1 showing (A) the nephrostomy tube and (B) the remnant left after attempted removal.

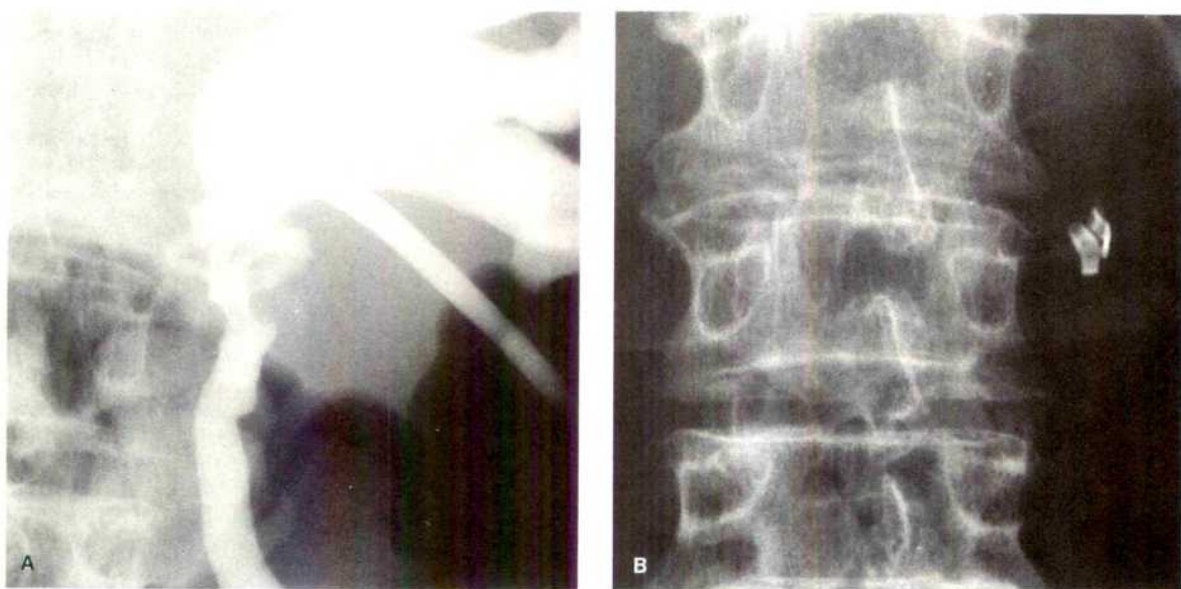


Fig. 2 X-ray in Case 2 showing (A) the nephrostomy tube and (B) the remnant left after attempted removal.

appears to have been due to the growth of tissue through the "wings" of the Malecot catheter. If a pigtail percutaneous nephrostomy tube had been used this complication would have been avoided.

We would advise that if nephrostomy tube drainage is considered necessary for more than 2 weeks, a pigtail nephrostomy tube should be used instead of a "winged" Malecot type.

References

- Lee, W. J., Smith, A. D., Cubelli, V. *et al.* (1987). Complications of percutaneous nephrolithotomy. *A. J. R.*, **148**, 177–180.
- Moskovitz, B., Vardi, Y., Wislang, M. *et al.* (1989). Fracture of double-J ureteric stents: a report of two cases. *Urol. Int.*, **44**, 241–243.

Requests for reprints to: L. H. Stewart, Department of Urology, Level 3, Belfast City Hospital, Lisburn Road, Belfast BT9 7AB.

Localisation of Intra-abdominal Testis by Magnetic Resonance Imaging

K. M. T. HO, M. L. NICHOLSON, M. L. WASTIE and P. W. WENHAM, *Departments of Surgery and Radiology, University Hospital, Nottingham*

Case Report

A 31-year-old man presented with 10-year history of aching and swelling in the left groin. His left testis was undescended and could not be felt in the inguinal canal or ectopically. A left inguinal hernia was noted. Magnetic resonance imaging (MRI) (Fig.) showed the testis in an ectopic position immediately to the left of the bladder.

At operation, a small indirect hernia sac containing the vas deferens was found in the left inguinal canal. The vas was traced to the testis in the peritoneal cavity. Orchiectomy was performed. Histology showed atrophic testicular tissue with no evidence of spermatogenesis or malignancy.

Comment

Localisation of the impalpable undescended testis is important to the surgeon because of 2 important complications: infertility and malignant change. Different localisation techniques can be summarised as venography and arteriography (vascular techniques), ultrasonography, computed tomography and magnetic resonance imaging (imaging techniques) and laparoscopy (visualisation).

Three studies evaluating the usefulness of MRI in patients with undescended testes have been reported. Fritzschke *et al.* (1987) in a retrospective study examined 15 undescended testes and 1 absent testis. Two were intra-abdominal. A testis missed by MRI was found at surgery to be near the gallbladder fossa. Kier *et al.* (1988) in a prospective study examined 14 patients with 15 undescended testes. Three testes were intra-abdominal. MRI interpretation was able to locate 1 of 3 prospectively and 2 of 3 retrospectively. The false negative occurred in a case of high abdominal testis in which the testis was located adjacent to a pelvic kidney. Troughton *et al.* (1990) studied prospectively 8 undescended testes; 6 were detected. The only intra-abdominal case was one in which both testes were situated in the abdominal cavity adjacent to the lateral border of the bladder.

MRI has the advantage of being non-invasive, non-ionising and capable of obtaining multiplanar images. It is a suitable method for the investigation of the undescended testis.

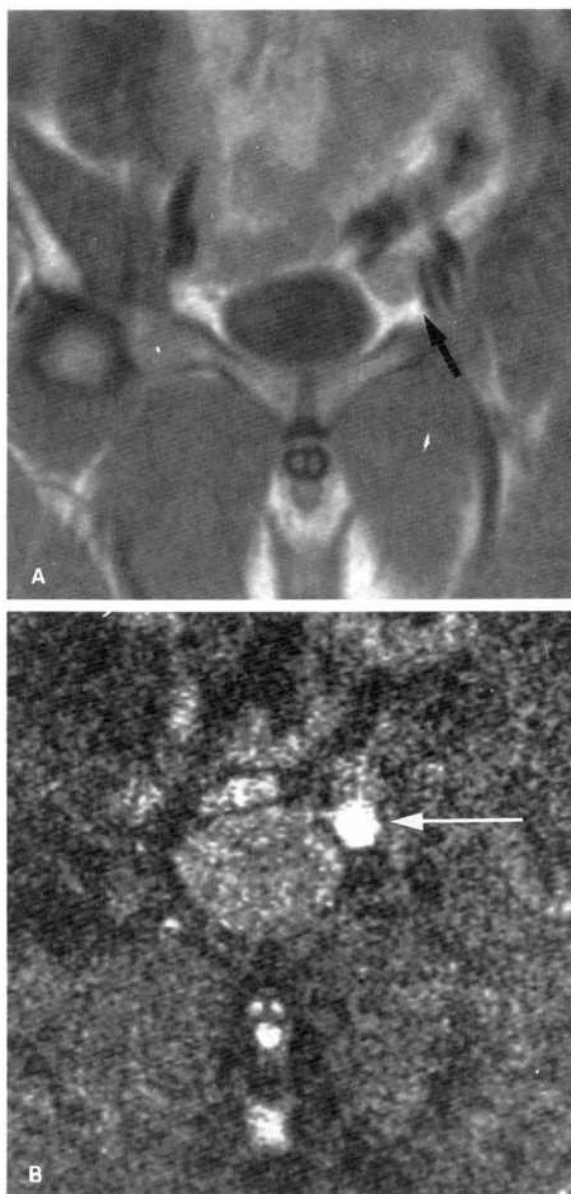


Fig. 1 (A) The testis (arrowed) shown on the left side of the bladder on the T1 weighted MRI scan. (B) With the STIR technique, the testis (arrowed) appeared as a bright spot.

References

- Fritzschke, P. J., Hricak, H., Kogan, B. A. *et al.* (1987). Undescended testis: value of MR imaging. *Radiology*, **164**, 169–173.
- Kier, R., McCarthy, S., Rosenfield, A. T. *et al.* (1988). Non palpable testes in young boys: evaluation with MR imaging. *Radiology*, **169**, 429–433.
- Troughton, A. H., Waring, J., Longstaff, A. *et al.* (1990). The role of magnetic resonance imaging in the investigation of undescended testes. *Clin. Radiol.*, **41**, 178–181.

Requests for reprints to: K. M. T. Ho, c/o Mr Wenham's secretary, Department of Surgery, E Floor West Block, University Hospital, Nottingham NG7 2UH.

Correspondence

re Eosinophilic prostatitis and prostatic specific antigen. S. Liu *et al.* *Br. J. Urol.*, **69**, 61–63, 1992.

We read with interest the above report of 3 patients with eosinophilic prostatitis. We note that this is a rare condition which may develop in the course of certain allergic disorders and may be associated with long-standing asthma. Histological findings are of eosinophilic infiltration with granulomata.

The association of asthma and eosinophilic tissue infiltrates is recognised (Churg-Strauss syndrome). The original 13 cases were described by Churg *et al.* (*Am. J. Pathol.*, **27**, 277–301, 1951). The clinical definition of the condition is based on a history of asthma, eosinophilia ($> 1.5 \times 10^9/\text{ml}$) and vasculitis affecting 2 or more extrapulmonary systems (Lanham *et al. Medicine*, **63**, 65–81, 1984). Allergic granulomatosis of the prostate and lower urinary tract has been described in Churg-Strauss syndrome (Chumbley *et al. Mayo Clin. Proc.*, **52**, 477–484, 1977). Indeed, in one case the illness began with acute urinary retention (Kekalis *et al. J.A.M.A.*, **188**, 963–967, 1964). Physical examination of the prostate in these cases was similar to that reported above. Respiratory symptoms may develop after the prostatitis. Conversely, in one reported case allergic granulomata of the prostate developed 7 years after resolution of an extensive pulmonary process (Chumbley *et al. Mayo Clin. Proc.*, **52**, 477–

484, 1977). These authors stress the importance of a urological history and careful digital examination of the prostate in patients with Churg-Strauss syndrome. Response to steroids is generally very rapid but in severe cases immunosuppression may be required.

The similarity between the 3 cases in the above article and those previously described is striking. With Churg-Strauss syndrome in mind a number of questions arise. Was there any evidence of allergic rhinitis or asthma in the current or past medical histories of these patients? Was there any evidence of other organ infiltration with eosinophils? What was the peripheral blood eosinophil count?

We feel it likely that the symptoms and signs of the patients described in this report may not represent isolated prostatic disease but a more generalised disorder, the other manifestations of which may yet arise. We suggest, therefore, that all 3 patients be kept under medical review with regular full blood count (plus white cell differential), chest X-ray examination and lung function assessments.

Yours faithfully,

A. Burns (Renal Unit, Hammersmith Hospital, London) and M. D. Dinneen (Department of Paediatric Urology, Hospital for Sick Children, London).

Notices

British Association of Urological Surgeons

President: J. C. Smith, MS, FRCS

Annual Meeting: Harrogate, 22–25 June 1993

Abstracts of contributions to be considered as either papers, posters or videos by the Programme Subcommittee of Council should be submitted on the special forms, which will be available from the BAUS Secretariat in October 1992. Completed forms, which should state clearly whether the submission is a paper, a poster or a video, must be returned to the Honorary Secretary by Friday, 8th January 1993.

Abstracts not on the special forms will NOT be considered.

All correspondence to: R. J. Morgan, FRCS, Honorary Secretary, British Association of Urological Surgeons, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

William Cook Travelling Fellowship

In 1990, William Cook Europe Limited generously offered an annual sum of £3000 to finance a minimum of three travelling fellowships each year. Candidates must be members of the British Asso-

ciation of Urological Surgeons. Applications should be made to the Honorary Secretary of BAUS by 1 February, giving the following information: the name of the centre to be visited, the reason for the visit and an estimate of the cost of travel and accommodation. Prior agreement to the visit must be obtained from the surgeon/hospital in question.

Applications will be considered by a BAUS Committee. Successful applicants will be required to submit a report on the experience gained in the centre visited.

The Surgitek Prize

The Prize consists of a fully sponsored visit to the American Urological Association Annual Five-day Meeting, together with a tour of Surgitek's manufacturing facility in Racine, Wisconsin. It is open to trainees in urology and consultants who are within 5 years of first appointment. Entrants should submit a written paper, which may be on any subject, but must be unpublished, and must not have been submitted previously for the Surgitek Prize, or other prizes. The winning entry will be the one which is considered to be "The most significant contribution to urology".

Entries will be judged by three members of BAUS Council nominated at the October meeting of Council. Papers should be submitted in triplicate to the Honorary Secretary by 1 January each year.

Diary

1992

- August 30–September 4 Ninth Congress of the International Pediatric Nephrology Association. Pediatric Urology Section. Jerusalem, Israel. Contact: Dr Amicur Farkas, Department of Urology, Shaare Zedek Medical Center, P.O.B. 3235, Jerusalem 91031, Israel.
- August 31 Workshop in Sacral Anterior Root Stimulation in Spinal Cord Injured Patients. Halifax, Nova Scotia, Canada. Satellite meeting of International Continence Society, September 1–4. Contact: Professor E. P. Arnold, Department of Urology, Christchurch Hospital, Christchurch, New Zealand.
- September 3–6 Tenth World Congress on Endourology and ESWL, Singapore. Contact: Secretariat, c/o Department of Urology, Singapore General Hospital, Outram Road, Singapore 0511.
- September 10–11 Pathobiology of the Prostate (Third Marmara Medical Days). Istanbul, Turkey. Contact: Department of Urology, Marmara University, School of Medicine, Tophanelioglu cad, No: 13–15, 81190 Istanbul, Turkey. Fax: 90 1 325 0323.
- September 14–18 Fifth World Meeting on Impotence and Eighth Symposium on Corpus Cavernosum Revascularization, Milan, Italy. Contact: Organizing Secretariat, OMNIA Meeting and Congressi, Via Senato 18, 20121 Milan, Italy.
- September 15–18 Euro-American Conference on Urological Cancer—Clinical and Biological Progress. Athens, Greece. Contact: Erasmus Conference Centre, International Congress Organizers, 227–229 Kifissias Avenue, Athens 145 62, Greece.
- September 17–18 Seventh Annual Paediatric Urology Course. Selwyn College, Cambridge. Contact: Mr R. H. Whitaker, Department of Urology, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ.
- September 21–23 VIII Andrology Course. Barcelona, Spain. Contact: Secretaría General, Fundación Puigvert, c/. Cartagena 340–350, 08025 Barcelona, Spain. Tel: 34.3 2355614. Fax: 34.3 4559938.
- September 23–25 Polish Association of Urology Annual Meeting. Wroclaw, Poland. Contact: Organizing Committee, Katedra i Klinika Urologii, 50–043 Wroclaw, Pl. 1-Maja 8, Poland. Tel: 347-59. Fax: 254 101.
- October 1–2 Continuing Medical Education and Training in Europe: the Future. London. Contact: Dr M. W. N. Nicholls, Conference Office, c/o Fellowship of Postgraduate Medicine, 6 St Andrew's Place, London NW1 4LB. Tel: (44) (0)71 935 5556. Fax: (44) (0)71 224 3219.
- October 1–3 Annual Meeting of the Swiss Society of Urology. Leysin, Switzerland. Contact: Prof. Dr P. Graber, Clinique de Chirurgie Urologique, Hôpital cantonal, CH-1211 Genève 4, or Prof. Dr D. Hauri, Urologische Klinik, Universitätsspital, CH-8091 Zürich.
- October 1–3 Fourth World Congress of VideoUrology. Monte Carlo, Monaco. Contact: Convergences—VideoUrology '92, 120 Avenue Gambetta, 75020 Paris, France. Telex: 216 911 F. Fax: (33-1) 40 31 01 65.

- October 3 Meeting of the Belgian Association of Urology. Bruges, Belgium. "Early diagnosis and treatment of localized carcinoma of the prostate". Contact: Dr J. Ampe, Department of Urology, A.Z. St Jan, Ruddershove 10, 8000 Brugge, Belgium.
- October 6-9 27th Annual Meeting of Egyptian Urological Association. Alexandria, Egypt. Contact: Dr Mamdouh Koraitim, Department of Urology, Faculty of Medicine, Alexandria University, Alexandria, Egypt.
- October 7-11 1992 Duke Urologic Assembly. "Contemporary Issues in Urology". Pinehurst, North Carolina. Contact: Linda Mace, Assembly Coordinator, Box 3707, Duke Medical Center, Durham, NC 27710, USA.
- October 9-10 BAUS Autumn Meeting, Swansea. Contact BAUS Office.
- October 15-16 European School of Oncology. 10th Anniversary Events. Milan, Italy. Contact: European School of Oncology, Via Venezian 18, 20133 Milan, Italy. Tel: (+39 2) 70635923-2364283. Fax: (+39 2) 2664662.
- November 1-4 Third International Workshop on Carcinoma *in situ* and Cancer of the Testis. Copenhagen, Denmark. Contact: Workshop Secretariat, c/o Professor N.E. Skakkebaek, University Department of Growth and Reproduction, Section 5064, Rigshospitalet, 9 Blegdamsvej, DK-2100, Copenhagen, Denmark.
- November 8-10 Fourth International Conference of the Society for Minimally Invasive Therapy. Dublin, Ireland. Contact: Professor J. Fitzpatrick, 47 Eccles Street, Dublin 2, Ireland. Tel: +353-1-308530. Fax: +353-1-300345.
- November 27-28 International Postgraduate Course on Reconstructive Surgery of the Lower Urinary Tract in Children. Amsterdam, The Netherlands. Contact: Conference Secretariat, Bureau PAOG Amsterdam, Tafelbergweg 25, 1105 BC Amsterdam, The Netherlands: Tel: +31 20-566 4801. Fax: +31 20-696 3228.
- December 4-5 Eighth International Steglitz Paediatric Surgical Congress. Berlin, Germany. Contact: Dr F. Schier, Kinderchirurgie, Univ.-Klinikum Steglitz, Hindenburgdamm 30, 1000 Berlin 45, Germany. Tel: (030) 798 4181 or 798 2909; Fax: (030) 798 4141.
- 1993
- January 26-29 Ninth Copenhagen Symposium on Endoscopic Urological Surgery. Herlev, Denmark. Contact: Dr F. Rasmussen, Department of Urology, Herlev Hospital, DK-2730 Herlev, Denmark.
- March 19-20 Second European Congress on Ambulatory Surgery. Brussels, Belgium. Contact: Dr C. De Lathouwer, Brussels One Day Clinic, Avenue du Duc Jean 71-73, B-1080 Brussels, Belgium. Tel: +322/424.1212. Fax: +322/425.7076.
- April 19-22 2nd Interamerican Meeting on Pediatric Urology. Vifia Del Mar, Chile. Contract: Dr Ricardo Gonzalez, 420 Delaware Street, S.E. Box 45, University of Minnesota Hospital, Minneapolis, Minnesota 55455, USA. Tel: 612 625-9117. Fax: 612 626-2458 or Dr Ricardo Zubieta, Esmeralda 678, 3 er Piso, Of. 303, Casilla 639, Santiago, Chile. Tel: 56-2-331. Fax: 56-2-391 085.
- May 16-20 American Urological Association, San Antonio Convention Centre, San Antonio, Texas.

Book Reviews

Urological Oncology: Dilemmas and Developments.

Edited by A. R. Alderson, R. T. D. Oliver, I. W. F. Hanham and H. J. G. Bloom. Pp. xvii+357. Chichester, New York, Brisbane, Toronto, Singapore: Wiley. 1991. Price: £65.00.

This book is dedicated to Professor Julian Bloom, who was the inspiration behind this work and who died before it could be published. There are 33 chapters under the main headings of adenocarcinoma of the kidney, carcinoma of the bladder, management of advanced prostate cancer, strategies of hormone treatment, second-line treatment, the testis, management of stage 1 malignant teratoma and conservative treatment of metastatic malignant teratoma. The authors are truly international and this gives an excellent perspective to the discussion. The chapters focus on principal controversies and those areas where new developments are important. This is a most readable book and will be much appreciated by urologists. It is a fitting tribute to Professor Bloom, whose own contributions to urological oncology made him one of the outstanding persons in this field in recent times.

The Diffusion of Two Technologies for Renal Stone Treatment Across Europe. (A Study of the Diffusion of Medical Technology in Europe Series). Series Editor: Barbara Stocking. Pp. 136. London: King's Fund Centre. 1991.

The title of this book is guaranteed *not* to attract the attention of most urologists. However, to ignore this and other similar titles in the Brave New World of the reformed National Health Service would be unfortunate. The book describes the introduction of the first expensive technology in urology, *i.e.* lithotripsy, and compares it with percutaneous nephrolithotomy. It is a multi-author text with a common theme: the need to control the introduction of expensive treatments into health care and to remove this control as far away from doctors as possible.

Is investment in this book likely to prove cost-effective for the urologist? In financial terms, no. However, an evening spent reading through it is well worth investment of time, since at the very least it will help us to understand the thought processes of health economists and enable us to enter into the debate about technology assessment and its introduction on a more rational basis.

Stone Surgery. By M. Marberger, J. M. Fitzpatrick, A. D. Jenkins and C. Y. C. Pak. Pp. 320. Edinburgh, London, Melbourne, New York, Tokyo: Churchill Livingstone. 1991. Price: £95.00.

There are now so many books and video tapes available which describe stone surgery that a new text must be of

sufficient quality to justify further investment by the individual or departmental library. The question is whether this book succeeds. It describes all aspects of modern stone management, including the now familiar anatomical discussions and design of an endourology suite, and a significant proportion of the book (over 15%) is devoted to pathophysiology and medical management.

There are 4 authors, although the text is predominantly written by one man. Thus his views predominate. A particularly attractive section is the guide to treatment selection in which two of the authors discuss the management of 21 different patients with stone disease. This section should be particularly useful for trainees who are contemplating higher examinations in urology. The book is well illustrated with line drawings and X-rays and the text is clear; the few endoscopic photographs are in black and white, which does not detract materially from the book.

Deficiencies? No reviewer with a major interest in stone disease can be entirely happy with the view that the best endoscopic management of ureteric stones is by ultrasound disintegration delivered through an 11.5 ureteroscope. It is surprising that the use of overhead fluoroscopy tubes and a 2-stage procedure is advocated as the optimum means of carrying out percutaneous surgery on the grounds that undercouch tubes and C-arms provide a poorer image quality. It is debatable too whether the ideal endourology suite today "combines ESWL and endourological techniques in one room preferably on one table", since this destroys the very flexibility which is so often required during stone management. These are small points, however, for this is a book written by surgeons for surgeons with a strong, clear chapter on medical management. The end result is a book which is both readable and of use to every practising urologist. At £95 it is worth every penny.

Genital Papillomavirus Infections. Modern Diagnosis and Treatment.

Edited by G. Gross, S. Jablonska, H. Pfister and H. E. Stegner. Pp. xxi+449. Berlin, Heidelberg, New York, London, Paris, Tokyo, Hong Kong, Barcelona: Springer-Verlag. 1990. Price: DM 148,-.

This volume records the Proceedings of the International Symposium on Genital Papillomavirus (HPV) Infections held in Hamburg in 1989. Although it emphasises the diagnostic and therapeutic aspects of HPV infections, it also contains much about their epidemiology, immunology and molecular genetics, including recent research work, and will obviously appeal more to dermatologists, gynaecologists and specialists in sexually transmitted diseases than to urologists.

The recommended first-line treatment for warts on the glans, frenum, corona, prepuce and shaft of penis is patient-applied, low-dose podofilox, which is one of the biologically active lignans contained in and purified from podophyllum resin. Urethral warts, not so common as

the others but no longer rare, respond poorly to locally destructive agents other than electrocoagulation or cryotherapy and frequently recur. Recurrences can be recognised early by the local application of 5% acetic acid, which whitens HPV-infected epithelium. For the more complicated warts, especially those in immunosuppressed patients, laser or interferon therapy may be needed.

The book has other messages for urologists who treat genital warts, reminding them that they must be familiar with and prepared to carry out all of the investigations appropriate to patients with sexually transmitted diseases and their sexual partners, and that in women HPV-induced infections can cause genital cancer.

Atlas of Bladder Pathology. By R. B. Bracken and B. Mackay. Pp. ix + 230. New York, Tokyo: Igaku-Shoin. 1991. Price: £68.00.

A number of excellent major works have been published in recent years in the field of urological pathology—including several comprehensive textbooks. The present publication is well produced and very well illustrated, mainly in black and white. The pathological illustrations, however, are supplemented by many fine cystoscopic photographs in colour. A somewhat unusual feature for a book of this type is the large number of electron micrograph pictures. This probably reflects the interests and expertise of one of the authors. Both tumours and non-tumourous conditions are well covered. The text is brief and avoids controversial topics. There is a selective list of up-to-date references.

As a collection of attractive illustrations dealing with the pathology of the urinary bladder this atlas fulfils its role and, as such, it is a useful addition to the major works which have been published in recent years.

Second C. J. Hodson Symposium on Reflux Nephropathy. Edited by R. R. Bailey. Pp. x + 79. Christchurch; printed by Design Printing Services. 1991.

Twenty papers dealing with all aspects of reflux nephropathy provide the core of this volume, which records the Proceedings of the Second C. J. Hodson Symposium on Reflux Nephropathy. Two papers originated from Brazil and the remainder from Australia and New Zealand, reflecting not only the location of the conference but also their continuing research into the problem of reflux nephropathy.

Emphasis is placed on diagnostic imaging, in particular the attempts to diagnose severe vesicoureteric reflux (VUR) before renal scarring occurs. It is recommended that when ultrasonography detects renal pelvic dilatation in pregnancy, repeat studies must be carried out after delivery and VUR excluded. Preliminary observations are presented on the use of a colour Doppler ultrasound which permits localisation of the ureteric orifices in the

posterior bladder wall and may provide a non-invasive screening method for refluxing ureters. Protocols for the investigation of children presenting with urinary tract infections and the screening of relatives of patients with VUR are presented and discussed. Emphasis is placed on non-invasive methods but the micturating cystourethrogram is still used as the gold standard in the younger age group. There is little emphasis, however, on the use of the radionuclide micturating cystourethrogram (either direct or indirect).

The main focus of discussion relates to the treatment of VUR and reflux nephropathy. The place of surgery has been eroded in recent years and there is no clear evidence that surgery for VUR leads to less renal scarring or less functional impairment than medical treatment. Surgery, however, is as effective as medical management and each has its advantages and disadvantages. The developing techniques of endoscopic management of VUR, while not solving the dilemmas of surgical treatment, provide a much simpler method of treating reflux. The role of the technique is still to be defined and the ideal injection material may still need to be found.

A great deal of information, some controversial, is packed into 80 pages, which makes this essential reading for all those who treat children or adults with vesicoureteric reflux or reflux nephropathy.

Erectile Dysfunction. Edited by U. Jonas, W. F. Thon and C. G. Stief. Pp. xiii + 325. Berlin, Heidelberg, New York, London, Paris, Tokyo, Hong Kong, Barcelona, Budapest: Springer-Verlag. 1991. Price: DM258.00.

This latest addition to an ever-increasing number of books on male erectile dysfunction seeks to provide a comprehensive overview of the subject. It is divided into 3 sections covering (i) anatomy, physiology and pathophysiology of erection, (ii) diagnosis and (iii) therapy of impotence. As with any publication of this kind, it inevitably has its strengths and weaknesses. Whilst the internationally recognised status of its mainly German contributors lends the book an authoritative tone, there is a considerable sense of déjà vu in many of the chapters. Nevertheless, there are some refreshing insights into the basic sciences, especially with regard to the neural innervation of cavernous tissue and neuropharmacology of erection. Unfortunately, the opportunity to produce a really worthwhile contribution to the area of ultrastructural changes in cavernosal tissue of impotent men has been missed by the lack of text in the 2 chapters devoted to it, downgrading them to a mere collection of pretty but meaningless illustrations.

The section on diagnosis tends to be didactic, with little critical appraisal of the clinical role of the various investigative tests described. There is undue emphasis on the neurophysiological assessment of the somatic pathways involved in erection which many now consider to be irrelevant. Similarly, the techniques of nocturnal

penile tumescence monitoring are described without any discussion about the place of this time-consuming investigation in the evaluation of the impotent male. Colour flow Doppler scanning, which is now considered to be state of the art in the non-invasive assessment of penile artery function, is only briefly touched upon, admittedly because of the time lag between manuscript submission and actual publication. However, the chapter on pharmaco-arteriography is excellent, testifying to the skills of the authors in this difficult area of radiological imaging.

Finally, the section on therapy is standard fare and again the proponents of venous leak surgery have not come up with a convincing case, stressing the need for some further fundamental research into the mechanisms of cavernosal venous occlusion in man.

Although this book is unlikely to generate a wide audience, it should appeal to those involved in impotence research, both for its coverage of the basic sciences as well as being a valuable source of references.

Incidental Carcinoma of the Prostate. Edited by J. E. Altwein, P. Faul and W. Schneider. Pp. xii + 272. Berlin, Heidelberg, New York, London, Paris, Tokyo, Hong Kong, Barcelona, Budapest: Springer-Verlag. 1991. Price: DM 118,-.

The increasingly controversial subject of incidentally diagnosed prostate cancer is covered by no less than 93 authors who contribute to 41 chapters within the 272 pages of this text. As might be expected, therefore, some accounts are no more than 2 to 3 pages long, whilst others cover their field more generously. Inevitably some concepts (e.g. the place of "second look" TUR) are discussed by a number of authors using the same reference material.

A note on the "refinements" embodied in the 1987 TNM revision will be helpful for 1978 "diehards". Problems of differentiation between A1 and A2 tumour are well brought out—1 cm³, 1%, 5%, 3 foci, etc; furthermore, a number of authors point out the fundamental lack of objective data if the gland is not later removed for complete study. Sections on histology, typical and atypical, are complemented by high quality reproductions.

As might be expected, personal prejudices colour some accounts. Debruyne *et al.* feel it is "obvious" that population screening by ultrasound is warranted; others would restrict it to high risk groups if tumour biopotential could be better defined. The editor summarises by suggesting that all younger males should undergo radical surgery, since irradiation and watch and wait are "on the way out". Zincke counsels a more cautious approach, quoting his series in which 29% of patients had no evidence of residual disease on section of the radically removed specimen.

This small text is easy to read and well presented, as one has come to expect from Springer-Verlag. Notwithstanding the inevitable restrictions of format, it is a well referenced and topical review of this important subject.

Urogynecology and Urodynamics. Theory and Practice. Third edition. Edited by D. R. Ostergard and A. E. Bent. Pp. xxix + 610. Baltimore, Hong Kong, London, Munich, Philadelphia, Sydney, Tokyo: Williams and Wilkins. 1991. Price: £73.00.

This 610-page book can be recommended for urological unit libraries. There are 45 contributors, mainly from North America. The 6 sections are on the Normal Urinary Tracts; Evaluation of Lower Tracts; Pathology and Treatment of Lower Urinary Tract Abnormalities; Detrusor Instability; Genuine Stress Incontinence and Miscellaneous Topics, including Effects of Drugs on the Urinary Tract.

The book is readable, well presented and comprehensive. The International Continence Society standardisation of terminology is used with slight modifications. Most chapters have a useful and succinct summary with useful chapters on Ambulatory Urodynamics and Surgical Procedures for General Stress Incontinence, but the surgical therapy for Detrusor Instability is incomplete. There is a useful section on the Effects of Drugs on the Lower Urinary Tract with, unfortunately, the withdrawal of Terodiline post-dating the printing of this chapter.

The data recording form for urogynaecology is clear and comprehensive. The volume emphasises that urinary incontinence is not a normal consequence of ageing but is manageable and curable in many instances.

Urolithiasis. A Medical and Surgical Reference. By M. I. Resnick and C. Y. C. Pak. Pp. ix + 375. Philadelphia, London, Toronto, Montreal, Sydney, Tokyo: Saunders. 1990. Price: £53.50; US\$ 75.00.

It has been difficult to keep pace with the spate of books on urinary tract stone disease that have flooded the market within the past ten years. Does yet another enlighten or confuse, is it more of the same or too much of a good thing? The Editors of this volume, either alone or in collaboration with others, have been responsible for a goodly proportion of these offerings. As the authors or co-authors of 15/17 chapters this, however, is very much their book. It is aimed at the practising clinician and is broadly in 2 sections: (1) the medical, dealing with the pathogenicity, biochemistry, therapeutics and preventive measures as seen through the eyes of a physician dedicated to the metabolic aspects of the disease, and (2) the surgical. The technology and the techniques, the prin-

ciples and the practice of a quite remarkable revolution in the surgical management of stones are now universally known and adopted and extensively written about. Future progress is likely to be confined to minor modulations and variations on a theme, orchestrated by the "stone gurus" with their soft and hardware merchants in tow with another part to sell.

This book opens with an introductory chapter that gives a historical and contemporaneous overview of the stone problem, albeit a predominantly North American one. A student new to the subject and unfamiliar with the literature will find the chapter on the physico-chemical processes of stone formation exceptional for its clarity, simplicity and eminently readable style. It deals separately with each of the stone-forming salts, never losing sight of the clinical significance; it would have been helpful if some of the provocative statements here had been backed up with references.

Succeeding chapters, each of which begins with a historical vignette, provide balanced, up-to-date and practical reviews of the putative "risk" factors of the idiopathic stone, *i.e.* hypercalciuria, hyperoxaluria and hypocitraturia. Pathogenetic mechanisms are well treated and explain what goes wrong and the investigative programmes outlined will help to define and treat recognisable biochemical abnormalities. Thiazides, of course, decrease calcium excretion, not "augment" it; this is a typographical error on page 40 that needs correction. The chapter on hyperoxaluria fails to mention the role of renal and hepatic transplantation, the only hope for the severe oxalosis of primary hyperoxaluria. The emphatic statement that Type 1 distal tubular acidification defect is the only form of renal tubular acidosis that is associated with nephrolithiasis is incorrect. A significant incidence of stone in proximal RTA has recently been reported. The authors' unique and authoritative experience on the investigation and medical management of the stone patient is encapsulated in this book and is a blueprint for a stone clinic. Some might feel, however, that too much emphasis is given to potassium citrate as the panacea for stone. There are a few typographical errors: insulin instead of inulin (page 108) and on page 213 it is the patient that is anaesthetised, not the kidney. Papyrus, incidentally, is an ancient manuscript, not a person.

Conventional open surgery for urinary tract stone has been almost relegated to the history books by the spectacular and rapid advances in minimally invasive and non-invasive surgical techniques. A 50-page chapter, therefore, on the surgery of kidney and ureteric stones, ponderously detailing general surgical and anaesthetic principles, techniques and complications, seems superfluous. In some countries and in some circumstances it may still be necessary and demands a place, but this is excessive. This aside, the chapters on endoscopic and percutaneous techniques and extracorporeal shock wave lithotripsy cover the state of the art, with some useful practical tips. On balance, this is one of the better books on the subject this decade.

Practical Urology in Spinal Cord Injury. (Clinical Practice in Urology Series). Edited by K. F. Parsons and J. M. Fitzpatrick. Pp. xii+145. London, Berlin, Heidelberg, New York, Paris, Tokyo, Hong Kong, Barcelona: Springer-Verlag. 1991. Price DM145,-.

This pleasantly produced and comprehensive little book has a wide spread of authorship, including contributions from many countries.

In the introduction, Professor Chisholm points out that there are many possible variations in the management of the urinary tract which may be considered correct. It might be expected, therefore, that in a multi-author publication of this kind there might be internal contradictions and inconsistencies, but these are pleasingly few. With the exception of minor considerations, repetition is similarly not a problem. The section on urodynamics is not well covered by the title of Practical Urology. The theory is present in abundance but a description of the practical steps is lacking. The advice in general indicates a standard of care for a paraplegic population which is not so stinted by resource inadequacy as it is for the population in Great Britain. The advice that an intravenous urogram should be done every year, repeated in 2 sections, seems over-indulgent even for the paraplegic population. Possibly the most interesting section concerns sexual function in both men and women, a subject that has been dealt with in a prudish and incomplete way in many earlier discussions on the rehabilitation and management of paraplegics. All matters, from psychology to pharmacology, are discussed in a sensitive and practical manner.

The use of sacral nerve stimulation and posterior deafferentation is included in the chapter entitled "Innovations and Future Possibilities". This seems a little unjust to a well established technique that belongs to the present. It is clear that the management of autonomic function in paraplegia is going to advance greatly over the forthcoming decades and this well produced book serves as a timely update, easily readable and well indexed into a comprehensive review of the literature. It should attain a wide audience amongst urologists and neurosurgeons, as well as those concerned with paraplegia care in spinal injury units.

Immunotherapy of Renal Cell Carcinoma. Clinical and Experimental Developments. Edited by F. M. J. Debruyne, R. M. Bukowski, J. E. Pontes and P. H. M. de Mulder. Pp. 141. Berlin, Heidelberg, New York, London, Paris, Tokyo, Hong Kong, Barcelona: Springer-Verlag. 1991. Price: DM88,-.

Immunotherapy as the fourth arm of cancer treatment has been through several cycles of exaggerated enthusiasm and excessive disillusionment since the beginning of

the twentieth century. The excessive enthusiasm of the last five years has been fuelled by the breakthrough in genetic engineering which has made available a wide range of cytokines, the natural regulators of immune response. Renal cancer is the tumour which has been at the forefront of this endeavour and this book provides a particularly useful summary of the last 5 years' work in this field in a brief and readable overview. Although entitled "Immunotherapy of Renal Cell Carcinoma", it also provides a useful update on other topics in renal cancer, *i.e.* current views on molecular genetics, a field which will undoubtedly impinge on immunotherapy in the future in terms of selecting the tumours that may be sensitive to immune manipulation, a most important direction for the future given that the response rate rarely exceeds 15% when unselected patients are treated.

The introduction by W. M. Lineham and the chapter by E. A. Klein are particularly useful for their reviews of the most critical experiments in genetics, *i.e.* those identifying mutation at a suppressor gene locus on chromosomes as being critical in the development of this tumour. The chapters on experimental studies and the clinical use of cytokines interferon alpha and interleukin-2 are comprehensive reviews of the current position. In addition, the summaries of the use of gamma interferon and TNF are extremely useful, as they emphasise the increasingly recognised fact that most cytokines have a bell-shaped dose response curve with high dose inhibition of response. The lack of impact of the extreme high tech fields of cellular therapy with lymphokine activated killer cells and tumour infiltrating lymphocytes as well as targeted monoclonal antibodies also emerges from close reading of the text. However, the most important deficit in the presentations is the lack of discussion on the frequency of spontaneous regression and the influence of

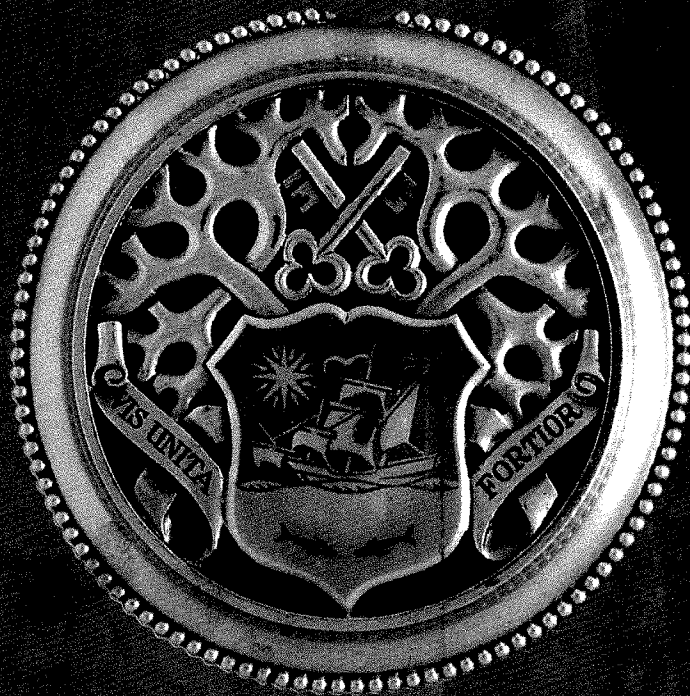
protocol selection criteria on response, which has been one of the main factors in making renal cancer a tumour which has raised false expectations so often in the past. Despite this defect, this book is an easily readable update of the present situation for both basic scientist and clinician, whether new to the field or not.

Clinical Atlas of the Kidney. Edited by J. D. Williams, A. W. Asscher, D. B. Moffat and E. Sanders. Pp. viii + 352. London, New York: Gower Publishing. 1991. Price: US\$ 195.00.

This integrated text and colour atlas of the histology, pathophysiology, diagnosis and treatment of renal diseases, which includes a substantial contribution on renal transplantation, is an extremely fine production. Although it is based on a previous work (Nephrology Illustrated, published in 1982 by Gower) and contains a few illustrations from that book, the text has been considerably expanded and is now written, not by the Editors, but by guest authors, all acknowledged experts in the subject of their contribution. The high quality of the text is enhanced by tables and algorithms and by the profusion of exquisite black and white and coloured photomicrographs and illustrations. A slide atlas based on the contents of the book is also available and should have a wide appeal to teachers of nephrology.

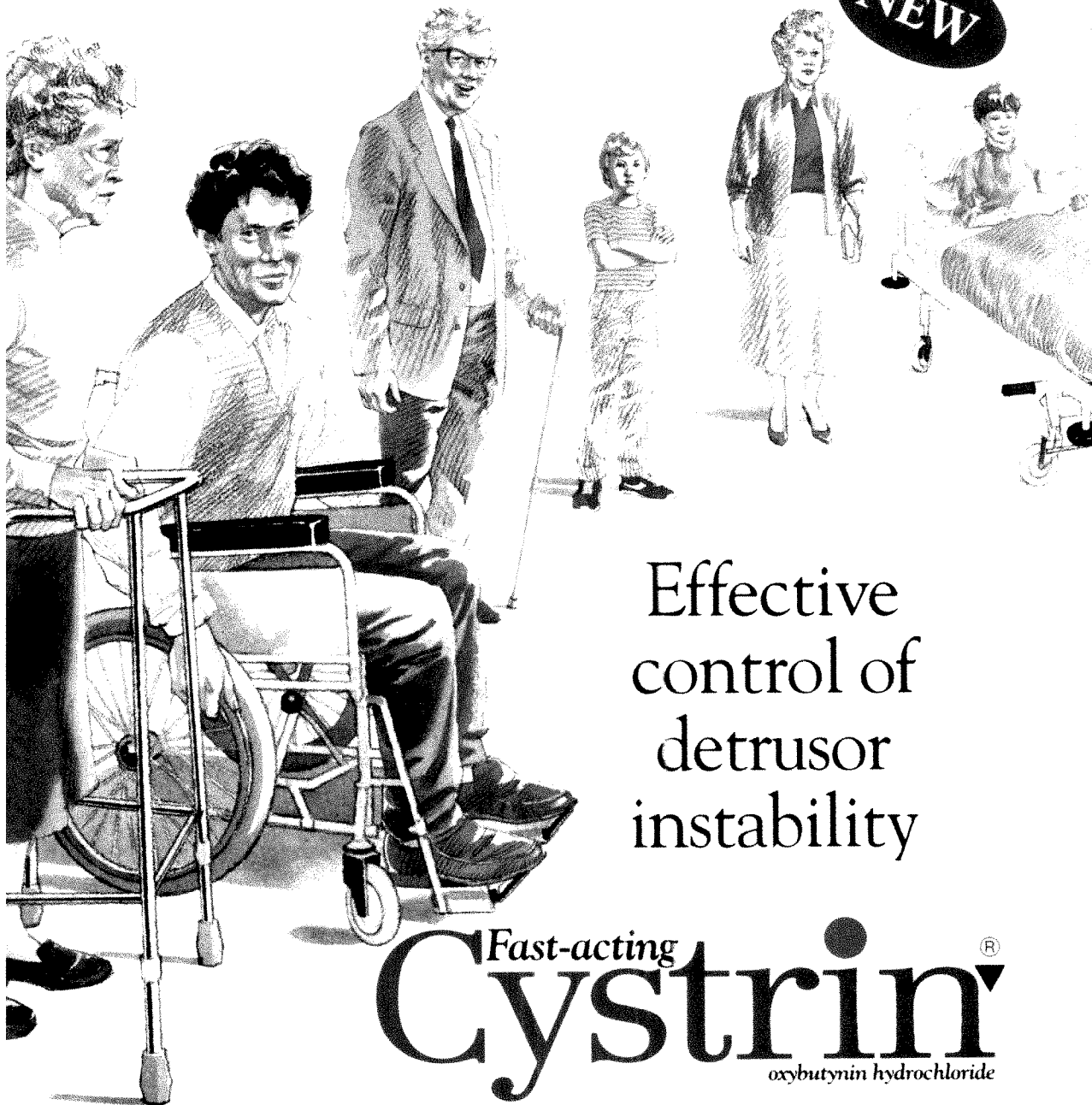
It is hoped that it will not be too long before a clinical atlas of similar magnificence on urology appears, though urologists will find much to interest them in this book and will not find a better reference volume on medical diseases of the kidney for their departments.

British Journal of UROLOGY



Chaucer Publishing

NEW



Effective control of detrusor instability

Fast-acting
Cystrin[®]
oxybutynin hydrochloride

NEW CONFIDENCE IN URGE INCONTINENCE
5mg b.d. or t.d.s.

CYSTRIN[®] PRESCRIBING INFORMATION

Presentation: Oxybutynin hydrochloride 5mg: Round, white tablets with breakline on one side and engraved "LH" on the other side. Oxybutynin hydrochloride 3mg: Round, white tablets with no markings. **Uses:** Urinary incontinence, urgency and frequency in patients with an unstable bladder due to idiopathic detrusor instability or neurogenic bladder disorders; also in nocturnal enuresis in conjunction with non-drug therapy. **Dosage and administration Adults:** The usual dose is 5mg orally two or three times a day. This may be increased to 5mg four times a day to obtain a clinical response provided that the side effects are tolerated. **Elderly:** A dose of 5mg twice a day is likely to be adequate, particularly if the patient is frail. **Children under 5 years of age:** Not recommended. **Children over 5 years (Neurogenic bladder):** The usual dose is 5mg orally twice a day; this may be increased to 5mg three times a day. (Nocturnal enuresis). The usual dose is 5mg two or three times a day, the last dose should be given before bedtime. **In children or the elderly,** the maintenance dose may be achieved by upward titration from an initial dose of 3mg orally twice a day. **Contra-indications:** Patients with obstruction of the bowel or significant degree of bladder outflow obstruction; intestinal atony; severe ulcerative colitis or toxic megacolon; myasthenia gravis; glaucoma. **Precautions:** Use with caution in the

frail elderly; patients with autonomic neuropathy; patients with hepatic or renal disease, or reflux oesophagitis. Symptoms of hyperthyroidism, coronary artery disease, congestive cardiac failure, cardiac arrhythmias, tachycardias and prostatic hypertrophy may be aggravated. As Cystrin may cause drowsiness or blurred vision, the patient should be cautioned regarding driving, operating machinery or performing hazardous work while taking this drug. **Pregnancy and Lactation:** Avoid in pregnancy unless there is no safer alternative. Cystrin should not be taken by breast-feeding mothers. **Side-effects:** The most frequently reported side effects are: dry mouth, constipation, blurred vision, nausea, abdominal discomfort, facial flushing and difficulty in micturition. **Interactions and Overdosage:** See Data Sheet. **Legal Category:** P.O. A. **Package Quantities and NHS Price:** 5mg packs of 100 tablets £28.67. 5mg pack of 500 tablets £143.35. 3mg packs of 100 tablets £17.20. **Product Licence Numbers:** 5mg tablets: PL 3433/0145. 3mg tablets: PL 3433/0146. Date of Preparation: January 1992.

Further information is available upon request from:
Farmitalia Carlo Erba Ltd., Italia House, 23 Grosvenor Road, St. Albans, Herts.
AL1 3AW. Tel. 0727 40041. Fax. 0727 40290.

BRITISH JOURNAL OF UROLOGY

Journal of the
British Association of Urological Surgeons
and the European Society of Paediatric Urology

Editor

*G. D. CHISHOLM

Honorary Treasurer

*J. P. PRYOR

Editorial Assistant

EDNA MacDONALD

Assistant Editors

R. J. MILLARD

*J. E. NEWSAM

*R. H. WHITAKER

Editorial Committee

Chairman J. H. STEYN*

E. P. ARNOLD, Christchurch
M. HANDLEY ASHKEN, Norwich
M. BHANDARI, Lucknow
*M. C. BISHOP, Nottingham
*J. P. BLANDY, London
A. C. BUCK, Glasgow
C. A. C. CHARLTON, Bath
D. J. DU PLESSIS, Pretoria
*J. M. FITZPATRICK, Dublin
J. C. GINGELL, Bristol
J. A. GOSLING, Hong Kong
*R. R. HALL, Newcastle upon Tyne
T. B. HARGREAVE, Edinburgh
*†K. HJÄLMÄS, Gothenburg
W. F. HENDRY, London
D. KIRK, Glasgow
V. R. MARSHALL, Adelaide

*A. R. MUNDY, London
D. E. NEAL, Newcastle upon Tyne
P. H. O'REILLY, Stockport
K. F. PARSONS, Liverpool
W. B. PEELING, Newport
A. RIZVI, Karachi
*R. J. MORGAN, London
†H. J. F. R. SERUCA, Lisbon
T. SHERWOOD, Cambridge
F. P. SOONAWALLA, Bombay
D. F. M. THOMAS, Leeds
H. N. WHITFIELD, London
J. E. A. WICKHAM, London
GORDON WILLIAMS, London
*R. E. WILLIAMS, Leeds
C. R. J. WOODHOUSE, London
P. H. L. WORTH, London

*Member of Executive Committee

†Member of E.S.P.U.

Former Editors

H. P. WINSBURY-WHITE, 1929-1948
D. BAND, 1949-1966
J. D. FERGUSON, 1967-1972
W. KEITH YEATES, 1973-1977

Churchill Livingstone 

Instructions to Authors

The *British Journal of Urology* welcomes original contributions on urological subjects from all parts of the world. Papers are accepted for consideration on the understanding that their contents have not been published in whole or in part elsewhere, that they are subject to editorial revision, and that the Editor is responsible for the order of publication. Papers on nephrology, of interest to the urological surgeon, are welcome. When relevant, authors must include a statement on the ethical aspects of their research.

Manuscripts. Papers should be submitted in Journal style. Failure to do so may lead to significant delays in publication. Papers should be typewritten in double spacing on A4 paper (21 × 29.7 cm) with a margin of at least 3 cm all round. Two copies of the manuscript and illustrations should be submitted and the author should retain a copy for reference.

Authorship. All authors must give signed consent to publication. Only those who have made a substantial contribution to the work should be designated as authors and a maximum number of five is preferred. Those who have made a smaller contribution should be recognised separately in the Acknowledgements section.

Original articles should be set out as follows, with each section beginning on a separate page: title page, summary, text, references, authors' page, tables, legends to illustrations.

The **title page** should give the following information: (1) title of article, (2) initials and names of each author, (3) the department and institution to which the work should be attributed.

The **summary** should consist of very brief statements about each of the main sections.

A list of 3 to 6 **key words** should be provided.

The **text** should be arranged as follows: (1) Introduction, (2) Patients and Methods, or Materials and Methods, (3) Results, (4) Discussion and Conclusions, (5) Acknowledgements.

References. The author is responsible for the accuracy of his references. When quoted in the text they should include the author's name and year of publication. In the case of 2 authors both names should be cited. If there are more than 2 authors, only the first author plus *et al.* should be quoted. The list of references at the end of the paper should be in alphabetical order and should give the names of *all* authors unless there are more than three, when only the first three should be given followed by *et al.* With journal references the following sequence should be observed: name(s); initials, date, title of paper, name of journal *abbreviated according to Index Medicus*; volume number, first and last page numbers. Thus

Morris, J. A., Oates, K. and Staff, W. G. (1986) Scanning electron microscopy of adenomatoid tumours *Br J Urol*, 58, 183–187.

References to books should be as follows:

Wright, F. S. and Howards, S. S. (1981). Obstructive injury. In *The Kidney*, ed. Brenner, B. M. and Rector, F. C. Second edition. Volume II. Chapter 38, pp. 2009–2044. Philadelphia: Saunders.

The **authors' page** should give the names of all authors, their qualifications and main appointment. Please indicate the name and address of the author to whom offprint requests should be made.

Tables should be kept to a minimum and laid out as simply as possible. Each should be typed on a separate sheet, numbered in Arabic numerals and should not duplicate information in the text.

Illustrations. Photographs and radiographs should be submitted in the form of half-plate prints (approximately 17 × 11 cm). All figures should be unmounted. The number of the illustration (in Arabic numerals), the author's name, and the "top" of the illustration should be indicated lightly in pencil on the back. The magnification of photomicrographs and details of staining techniques should be given. Lettering on figures must be indicated on a transparent overlay. Illustrations in colour cannot be accepted unless the author is willing to cover the cost.

Points of Technique and Case Reports should not exceed 250 words, 2 illustrations and 3 references. In **Case Reports** the sections should be (1) Case Report, (2) Comment, (3) References.

Proprietary names of drugs, instruments, etc., should be indicated by the use of initial capital letters.

Abbreviations and units. All measurements should be expressed in S.I. units except blood pressure which will continue to be expressed in mmHg. For more detailed recommendations authors may consult the Royal Society of Medicine publication entitled *Units, Symbols and Abbreviations: A guide for Biological and Medical Editors and Authors*.

Correspondence. Questions or comments concerning recently published papers may be sent to the Editor, who will refer them to the authors. The readers' comments and authors' replies may subsequently be published together in the Correspondence column.

Address. All editorial communications, including books for review, should be addressed to the Editor, Professor G. D. Chisholm, Western General Hospital, Edinburgh EH4 2XU.

Offprints. Twenty-five free offprints are supplied to the author to whom offprint requests are to be made. Order forms will be sent with the proofs for correction, all of which should be returned to the publishers within 7 days of receipt.

Subscriptions. The journal is published monthly by Churchill Livingstone. Institutional rate for 1992 is £90.00 (UK), £100.00 (overseas) or \$180.00 (USA), the Trainee rate is £39.00 (UK), £42.50 (overseas) or \$76.50 (USA) per annum, post free, for non members. Second class postage is paid at Rahway NJ Postmaster: send USA address corrections to British Journal of Urology, c/o Mercury Airfreight International Ltd Inc, 2323 Randolph Avenue, Avenel, New Jersey 07001.

This journal is indexed, abstracted and/or published on line in the following media: Adonis, Colleague (online), Current Awareness in Biological Sciences, Current Contents, Excerpta Medica, Biological Abstracts, UMI (Microfilms), BRS Colleague (full text), British Medicine, Chemical Abstracts, Modern Medicine, Index Medicus, NMLUIS Reference Up Date and UMI (Disk).

Subscription enquiries: Longman Group U.K. Limited, Subscriptions (Journals) Department, P.O. Box 77, Fourth Avenue, Harlow, Essex CM19 5BQ. Telephone 0279 623760.

Note to Users in the USA. Authorisation to photocopy items for internal or personal use is granted by the copyright holder provided that the fee of \$2 per copy plus \$1.50 per page is paid directly to Copyright Clearance Center, 27 Congress Street, Salem, MA 01970, USA. For more information, please contact CCC. For territories outside North America, permission should be sought direct from the copyright holder. This consent does not extend to other kinds of copying, such as copying for general distribution, for advertising and promotional purposes, for creating new collective works, or for resale.

0007-1331/92/\$2 per copy \$1.50 per page

Copyright © 1992 British Journal of Urology. All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, without the prior permission of the copyright owner, or a licence permitting restricted copying in the United Kingdom issued by the Copyright Licensing Agency Ltd, 90 Tottenham Court Road, London W1P 9HE.

Printed on acid-free Fineblade Smooth 100 gsm paper. The publisher's policy is to use paper manufactured from sustainable forests.

British Journal of Urology

Volume 70 No 3 Pages 225–344 September 1992

Contents

Review

Haemostasis in Urology: Mechanism and Pharmacology

T. P. Briggs, C. Parker, K. Anson and R. A. Miller 225

Original Articles

Adult Wilms' Tumour: Review of 14 Patients

Grant Williams, R. A. Colbeck and N. F. C. Gowing 230

Acquired Cystic Disease of the Kidney and Renal Carcinoma in Haemodialysis Patients: Ultrasonographic Evaluation

I. Sasagawa, Y. Terasawa, K. Imai, H. Sekino and H. Takahashi 236

Agglomeration of Calcium Oxalate Monohydrate in Synthetic Urine

F. Grases, L. Masárová, O. Söhnle and A. Costa-Bauzá 240

Urological Complications Following Live Donor Kidney Transplantation: Effect of Urinary Schistosomiasis

A. A. Shokeir, M. A. Bakr, T. A. El-Diasty, M. A. Sobh, F. E. Moustafa, A. E. El-Agroudi and M. A. Ghoneim 247

Management of Impacted Upper Ureteric Calculi: Results of Lithotripsy and Percutaneous Litholapaxy

A. Srivastava, R. Ahlawat, A. Kumar, R. Kapoor and M. Bhandari 252

Management of Hydatid Cysts of the Urinary Tract

S. D. Shetty, A. Al-Saigh, A. I. A. Ibrahim, K. P. Patil and C. L. Bhattachan 258

The Actions of Extracellular Magnesium on Isolated Human Detrusor Muscle Function

B. S. I. Montgomery, P. J. Thomas and C. H. Fry 262

Vesica Fellea—A New Substitute for the Bladder? An Experimental Study

T. Güçer and H. Özkardeş 269

Outcome in Carcinoma *in situ* of Bladder Treated with Intravesical Bacille Calmette-Guérin

S. J. Harland, C. R. Charig, W. Highman, M. C. Parkinson and P. R. Riddle 271

Laparoscopic Pelvic Lymph Node Dissection

W. G. Bowsher, A. Clarke, D. G. Clarke and A. J. Costello 276

Is Urethral Pressure Profilometry Useful in the Pre-operative Assessment of Benign Prostatic Hyperplasia?

C. R. Chapple, S. W. Coppinger and R. T. Turner-Warwick 280

A 12-Week Placebo-controlled Double-blind Study of Prazosin in the Treatment of Prostatic Obstruction due to Benign Prostatic Hyperplasia

C. R. Chapple, M. Stott, P. H. Abrams, T. J. Christmas and E. J. G. Milroy 285

Prostate Specific Antigen and Bone Scan Correlation in the Staging and Monitoring of Patients with Prostatic Cancer

P. D. Miller, I. Eardley and R. S. Kirby 295

Levels of Prostate Specific Antigen that Predict Skeletal Spread in Prostate Cancer M. L. Pantelides, S. P. Bowman and N. J. R. George	299
Treatment of Advanced Localised Prostatic Cancer by Orchiectomy, Radiotherapy, or Combined Treatment A Medical Research Council Study G. J. Fellows, P. B. Clark, L. L. Benyon, J. Boreham, C. Keen, M. C. Parkinson, R. Peto and J. N. Webb (Urological Cancer Working Party—Subgroup on Prostatic Cancer)	304
Prostate Cancer—the Impact of Irradiation on Urinary Outlet Obstruction N. Green, D. Treible, H. Wallack and H. S. Frey	310
Screening for Bacteriuria in Urological Patients using Reagent Strips Sarah J. Mills, M. Ford, F. Kate Gould, Sally Burton and D. E. Neal	314
Paediatric Urology	
Clinicopathological Study of Nephroblastomas in Ibadan E. E. U. Akang, J. U. Okpala, Y. Iliyasu and J. Lawani	318
Natural History of Obstructed and Pseudo-obstructed Megaureters Detected by Prenatal Ultrasonography A. M. K. Rickwood, L. D. Jee, M. P. L. Williams and P. A. M. Anderson	322
Case Reports	
Unusual Presentation of Adult Posterior Urethral Valve R. Kapoor, A. Tewari and V. K. Mishra	326
Pelvic Lipomatosis or Pericystitis Plastica? C. F. Heyns and F. J. Allen	327
Mesothelioma of the Tunica Vaginalis of the Testis J. G. Noble, A. Watkins, M. E. Chappell and A. D. Heath	328
Leukaemic Infiltration, Paracoccidioidomycosis and Nodular Hyperplasia of the Prostate C. R. Melo, I. S. Melo and C. T. Cerski	329
Ureteric-Anal Canal Fistula Secondary to Ureteric Calculus U. V. Sathaye, K. V. Shah and K. P. Parikh	330
Leiomyoma of the Renal Pelvis A. O'Brien, B. Sinnott, P. McLean and G. D. Doyle	331
Ureterocolic Fistula due to Impacted Ureteric Stone K. P. Patil, S. D. Shetty, N. Anandan and A. Ibrahim	332
Choriocarcinoma Arising in Transitional Cell Carcinoma of the Bladder A. L. Fowler, Elizabeth Hall and G. Rees	333
Correspondence	335
Notices	341
Diary	342
Erratum Volume 69 No 1 January 1992 page 99 Vesicostigmoid Fistula as an Incidental Finding Accompanying Bladder Cancer N. E. Stravropoulos <i>et al.</i>	344

REVIEW

Haemostasis in Urology: Mechanism and Pharmacology

T. P. BRIGGS, C. PARKER, K. ANSON and R. A. MILLER

Department of Urology and Minimally Invasive Surgery, Whittington Hospital, London

Inadequate haemostasis remains one of the most important causes of morbidity and mortality following urological surgery. The advent of minimally invasive techniques and day-case surgery have highlighted the importance of haemostasis. The possibility of contaminated blood products is a further stimulus for avoiding unnecessary transfusion of blood. In this review the principles of haemostasis and the pharmacology of its enhancement are reviewed.

Background Physiology

Fine balance of the coagulation and fibrinolytic system allows blood to flow freely around the body. A basic understanding of both systems is necessary. There are 3 phases of the coagulation system:

- (a) The vascular phase.
- (b) The platelet phase.
- (c) The coagulation phase.

Following surgical or traumatic injury the vascular phase results in vasoconstriction, causing reduced blood flow to the damaged region. Simultaneously, platelet aggregation occurs in the damaged area. This function of the platelets is dependent on a plasma protein called the Von Willebrand factor. Amplification of the clotting cascade occurs to produce a stable fibrin web. The fibrinolytic system, with the production of plasmin, limits fibrin formation to the area of local damage (Fig.).

It is important to identify patients at possible risk pre-operatively. Apart from those with hereditary coagulation disorders such as haemophilia or

Von Willebrand's disease, other factors such as liver disease, anticoagulant drugs or thrombocytopenia may contribute to severe peri-operative bleeding. Thrombocytopenia may be due to failure of platelet production (due to drugs, chemicals or viral infection), part of a general bone marrow failure, or to increased destruction of platelets. Aspirin, widely prescribed to prevent thrombosis by preventing platelet aggregation, should be stopped 10 days prior to surgery (Watson *et al.*, 1990). Urokinase, a powerful plasminogen activator, is present in normal urine (Schmutzler and Furstenberg, 1966). This may cause dissolution of the fibrin mesh and cause secondary haemorrhage after urological surgery (Anderson *et al.*, 1968).

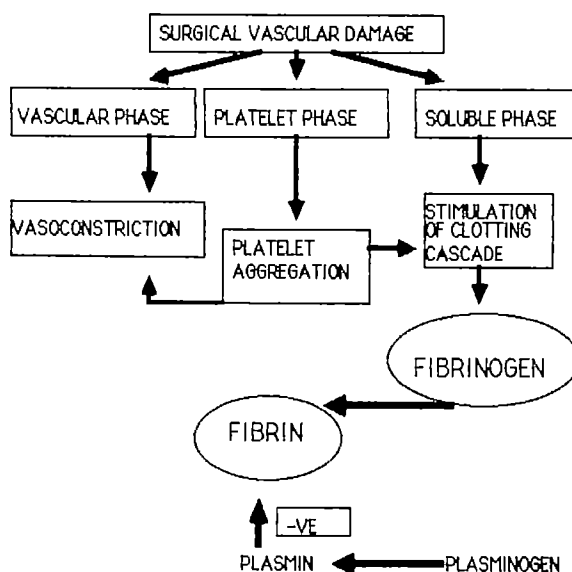


Fig. Summary of the haemostatic and fibrinolytic systems.

Open Surgery

During open surgery, bleeding may be difficult to control either because of its site or its nature (capillary, venous oozing) or because of the consistency of the tissue in the operative field. In these circumstances local haemostatic agents may be useful. Materials that have been used include absorbable haemostatic gelatin sponge, cellulose, collagen and fibrin glue. Haemostatic activity is an inherent property of collagen. This is largely dependent on the basic helical structure of this protein and the availability of certain amino acid groups which stimulate the clotting cascade. Platelets coming into contact with the collagen aggregate, with the subsequent formation of a clot. Oxidised cellulose also acts by a physical method, by stimulating blood coagulation on contact with blood. Both collagen and cellulose are good at controlling minor oozing from small veins, but not from larger arteries with a significant intravascular pressure. Oxidised cellulose has a low pH and can interfere with wound healing and should not be used in surface wounds (Swinyard and Pathak, 1980).

Thrombin can be applied topically but should never be injected into tissue because of the possibility of embolisation. Swabs impregnated with calcium alginate release calcium ions on contact with blood in exchange for sodium ions, stimulating platelet activation and whole blood clotting (Blair *et al.*, 1990).

Fibrin glue has many uses in urology (Vecsey, 1986), not only for its haemostatic properties but also as a sealant in ureteric surgery (Schultz and Christiansen, 1985), in reconstructive urethral surgery (Spehr, 1986) and the repair of urinary bladder fistulae both endoscopically (Frea *et al.*, 1986) and transperitoneally (Urlesberger and Henning, 1986). It is made by combining a solution of fibrinogen concentrate and factor XIII with a solution of thrombin and calcium. The thrombin is bovine in origin and the fibrinogen, originally of pooled human plasma with a risk of hepatitis and AIDS, can now be obtained from pre-screened single donor plasma. It may be applied topically or via a fine atomising spray (Joyce *et al.*, 1989) or by intraparenchymal injection (Hauser, 1989). Its use in renal trauma has been reported by Kram *et al.* (1989), with good results in parenchymal injuries. In partial nephrectomy (Henning and Urlesberger, 1986) and pelvic surgery (Weintensfelder *et al.*, 1986) it has been used in combination with collagen fleece. As well as providing haemostasis it dispenses

with the need for using traumatising needles on renal parenchyma.

Endoscopic Surgery

In endoscopic surgery topical materials become less practical, but locally injected drugs can be effective.

Adrenaline, a sympathomimetic, has both alpha and beta effects. The ideal vasoconstrictor would have alpha effects only (Jastak and Yagiela, 1983). One of these alpha effects is vasoconstriction. It has been used for some time in combination with local anaesthetics to reduce the vascularity of the operative field and to reduce the absorption of the local anaesthetic. It has found use mainly in upper gastrointestinal endoscopy, where the method of action of injected adrenaline is thought to be vasoconstriction, local tamponade, platelet aggregation and promotion of thrombus formation. It has been used in prostatic surgery (Birch *et al.* 1990) in conjunction with sedoanalgesia, providing a better field of vision, allowing accurate haemostasis and a reduction in peri-operative bleeding. The improved visibility increases the speed of the operation, which is an important factor in sedoanalgesia. Felypressin is thought to cause vasoconstriction on the venular side of the circulation and although it has no arrhythmogenic potential with its obvious attraction, it provides poor haemostasis, probably because it does not constrict arterioles (Jastak and Yagiela, 1983). The addition of adrenaline to local anaesthetics reduces the absorption of the local anaesthetic from its injected site into the systemic circulation. Larger doses of some local anaesthetics can be used when combined with vasoconstrictors (Table 1). The dose of adrenaline that is necessary to produce these effects is poorly understood. Bieter (1936) showed that for infiltration anaesthesia 1:200,000 adrenaline prolonged the action of procaine for the longest time, but 1:500,000 still provided good prolongation of anaesthesia (Table 2). In certain locations higher doses of adrenaline appear necessary, such as the oral mucosa. In dentistry the favoured dose is 1:80,000.

Sclerotherapy has proved itself in oesophageal varices and gastric haemorrhage but not in urology. The mechanism of action is worth considering. The agents used are monoethanolamine oleate, a sodium salt of the fatty acids of cod liver oil, sodium tetradecyl sulphate and polidocanol. Polidocanol is used in combination with adrenaline. These solutions work by damaging the endothelium of the vessel wall with subsequent thrombosis. Alcohol

Table 1 Drugs Affecting the Different Phases of Haemostasis

Vascular	Blood	Local
Adrenaline	Platelets	Alginate
Alcohol	Fibrinogen	Fibrin glue
Vasopressin	FFP	Cellulose
Sclerosants:	Aprotinin	Collagen
(STD)*	DDAVP	Thrombin
(MEO)†	Tranexamic acid	
(polidocanol)	Ethamsylate	
	E-aminocaproic acid	

*Sodium tetradecyl sulphate.

†Monoethanolamine oleate.

Table 2 Adrenaline Doses with Local Anaesthetics

Concentration of adrenaline (mg/ml) (parts/thousand)		Maximum dose (mg)* (ml)	
0.02	1/50,000	0.20	10
0.01	1/100,000	0.20	20
0.005	1/200,000	0.20	40
0.0025	1/400,000	0.20	80

*(British National Formulary maximum dose is 0.5 mg).

98% works by causing endothelial damage by dehydration (Sugawa *et al.*, 1986). Fibrin glue has been used after transurethral prostatectomy (TURP) with a specially designed double balloon catheter. The fibrin glue was dispersed around the prostatic cavity and the distal balloon inflated for 3 min (Frimodt-Moller *et al.*, 1988). Only 10 patients were reported in this pilot study.

Endoscopic surgery involving percutaneous tracts can be complicated by severe haemorrhage. Fibrin glue has its use, again in combination with collagen fleece, wrapped around a small catheter which can be placed down the sheath prior to removal. The small size catheter was also more comfortable for the patient (Pfaff *et al.*, 1987). Gazelle *et al.* (1990) reported the use of a thrombin-coated protein polymer sheath in enhancing haemostasis at percutaneous biopsy, which is clearly important in full thickness renal biopsies. Arterial occlusion devices (which are beyond the scope of this review) have also been used to stop haemorrhage after percutaneous surgery. They have also been employed to reduce vascularity prior to tumour surgery. Materials used for embolisation include autologous tissue and clot, metallic and silastic spheres, cotton tails and wool coils (Gianturco *et al.*, 1975).

Systemic Drugs

Systemically acting drugs such as aprotinin (Trasylol), desmopressin (DDAVP), ethamsylate (Dicycylene), epsilon aminocaproic acid and tranexamic acid (Cyklokapron) have all been used in urological surgery with varying success. Aprotinin is a protein inhibitor derived from bovine organs. It has 58 amino acids and its ability to inhibit a large range of serine proteinases accounts for most of its activity (Fritz and Wunderer, 1983). In prostatic surgery large amounts of plasminogen activators can be released, so that a possible role can be identified. Aprotinin is also known to inhibit human urokinase, if only weakly (Fritz and Wunderer, 1983). The type of response to aprotinin is dose-dependent. Studies using aprotinin and epsilon aminocaproic acid in prostatic surgery were not promising. However, only low dose aprotinin was used (between 500,000 and 700,000 units over 24–48 h) (Schmutzler and Furstenberg, 1966; Pearson, 1969). In recent studies in cardiac surgery, patients received high dose aprotinin, 5 million units over the course of the operation. This resulted in a marked reduction of 50% in post-operative blood loss (Bidstrup *et al.*, 1989).

Vasopressin has been used in bleeding oesophageal varices with great success by causing vasoconstriction of splanchnic arterioles and a reduction in portal venous pressure (Toft *et al.*, 1984). However, desmopressin (DDAVP), an analogue of vasopressin, has been found to be useful in patients with Von Willebrand's disease by reducing the bleeding time. Unlike vasopressin, desmopressin has little vasoconstrictor action. Its mode of action is thought to be by causing Von Willebrand factor to move from intracytoplasmic stores to the luminal surface of endothelial cells (Bolan and Alving, 1990). Von Willebrand factor is essential for platelet function in primary haemostasis (Mannucci *et al.*, 1977). After repeated doses it does exhibit tachyphylaxis, as it stimulates release but not resynthesis of Von Willebrand factor (Drouet *et al.*, 1989). It may be administered intravenously, subcutaneously or intranasally (the intranasal dose being 10 times the recommended intravenous dose). In normal subjects DDAVP has been shown to reduce blood loss in patients undergoing cardiac and orthopaedic surgery. As pointed out by Salzman (1990), a reduction in blood loss will occur only when the blood loss could be expected to be large and not in uncomplicated surgery in the normal patient.

Urokinase, a plasminogen activator, has already been mentioned. Drugs inhibiting its action may

play an important role in haemostasis. Epsilon aminocaproic acid competitively inhibits the activation of plasminogen to plasmin. It has been used as a post-operative bladder irrigant in transurethral resection of the prostate (TURP) but did not reduce the blood loss (Sharifi *et al.*, 1984). Madsen and Straunch (1966) found that intravenous epsilon aminocaproic acid did reduce post-operative blood loss but not peri-operative blood loss in TURP. Tranexamic acid (AMCA) has the same mode of action as epsilon aminocaproic acid but is 8 times more potent. Fibrinolysis stimulated by urokinase may be the initiator of secondary haemorrhage in the urinary tract and Miller *et al.* (1980) have shown that the incidence of secondary haemorrhage can be reduced by using tranexamic acid after TURP.

After some initial success with ethamsylate, further studies (Towler and Valerio, 1978; Lyth and Booth, 1990) have shown no difference in blood loss after TURP with ethamsylate administration.

Fresh frozen plasma, platelets and cryoprecipitate are still necessary in many forms of surgery, especially when multiple transfusions have been given or when, in the face of bleeding, clotting screens have shown abnormal results.

Urologists may benefit from these ancillary techniques of haemostasis, especially when used in conjunction with careful peri-operative haemostasis and avoidance of identifiable factors such as aspirin ingestion. The use of local agents such as adrenaline and fibrin glue can increase the speed and safety of urological surgery and may potentiate day-case urology by further reducing the risk of haemorrhage.

References

- Anderson, L., Nilsson, I. N., Colleen, S. *et al.* (1968). Role of urokinase and tissue activator in sustaining bleeding and the management thereof with EACA and AMCA *Ann N Y Acad. Sci.*, **146**, 642–658.
- Bidstrup, B. P., Royston, D. and Taylor, K. M. (1989). Reduction in blood loss and blood use after cardiopulmonary bypass with high dose aprotinin (Trasylo) *J Thorac Cardiovasc Surg*, **97**, 364–372.
- Bieter, R. N. (1936). Applied pharmacology of local anaesthetics *Am. J. Surg*, **34**, 500–510.
- Birch, B. R. P., Anson, K. M. and Miller, R. A. (1990). Sedoanalgesia in urology: a safe, cost-effective alternative to general anaesthesia. A review of 1020 cases *Br J Urol.*, **66**, 342–350.
- Blair, S. D., Jarvis, P., Salmon, M. *et al.* (1990). Clinical trial of calcium alginate haemostatic swabs *Br J Surg*, **77**, 568–570.
- Bolan, C. D. and Alving, B. M. (1990). Pharmacologic agents in the management of bleeding disorders *Transfusion*, **30**, 541–551.
- Drouet, L., Scrobohaci, M. L., Boudaoud, S. *et al.* (1989). Desmopressin (DDAVP) a powerful general hemostation agent? *Nouv. Rev. Fr. Hematol.*, **31**, 163–165.
- Freca, B., Cocimeno, V., Mosele, G. *et al.* (1986). The use of fibrin sealant in the treatment of urinary bladder fistulae. In *Fibrin Sealant in Operative Medicine, Gynaecology and Obstetrics—Urology*, ed. Schall, G. and Redl, H. Volume 3. Pp. 141–142. Berlin, Heidelberg: Springer-Verlag.
- Frimodt-Moller, C., Holm-Nielsen, A. and Gammelgaard, J. (1988). Transurethral application of fibrin glue following transurethral prostatectomy. A pilot study. In *Fibrinklebung in der Endoskopie*, ed. Manegold, B. C. Pp. 181–184. Berlin, Heidelberg: Springer-Verlag.
- Fritz, H. and Wunderer, G. (1983). Biochemistry and application of aprotinin, the kallikrein inhibitor from bovine organs. *Drug Res.*, **33**, 479–494.
- Gazelle, G. S., Haaga, J. R. and Neuhauser, D. (1990). Hemostatic protein-polymer sheath: new method to enhance hemostasis at percutaneous biopsy. *Radiology*, **175**, 671–674.
- Gianturco, C., Anderson, J. H. and Wallace, S. (1975). Mechanical devices for arterial occlusion. *A J R.*, **124**, 428–435.
- Hauser, C. J. (1989). Hemostasis of solid viscus trauma by intraparenchymal injection of fibrin glue. *Arch. Surg.*, **124**, 291–293.
- Heinling, K. and Urlesberger, H. (1986). Partial nephrectomy with fibrin sealant. In *Fibrin Sealant in Operative Medicine, Gynaecology and Obstetrics—Urology*, ed. Schlag, G. and Redl, H. Volume 3. Pp. 105–110. Berlin, Heidelberg: Springer-Verlag.
- Jastak, J. T. and Yagiela, J. A. (1983). Vasoconstrictors and local anaesthesia: a review and rationale for use. *J. Am. Dent. Assoc.*, **107**, 623–630.
- Joyce, D. H., McGrath, L. B. and Gonzalez-Lavin, L. (1989). A method of applying fibrin sealant using an atomizing needle. *Ann Thorac Surg.*, **47**, 320.
- Kram, H. B., Ccampo, H. P., Yamaguchi, M. P. *et al.* (1989). Fibrin glue in renal and urethral trauma. *Urology*, **33**, 215–218.
- Lyth, D. R. and Booth, C. M. (1990). Does ethamsylate reduce haemorrhage in transurethral prostatectomy? *Br J Urol.*, **66**, 631–634.
- Madsen, P. O. and Straunch, A. E. (1966). The effect of aminocaproic acid on bleeding following transurethral prostatectomy. *J. Urol.*, **96**, 255–256.
- Mannucci, R. M., Pareti, F. I., Ruggeri, Z. M. *et al.* (1977). 1-Deamino-8-D-Arginine vasopressin: a new pharmacological approach to the management of haemophilia and Von Willebrand's disease. *Lancet*, **1**, 869–872.
- Miller, R. A., May, M. W., Headry, W. F. *et al.* (1980). The prevention of secondary haemorrhage after prostatectomy: the value of anti-fibrinolytic therapy. *Br. J. Urol.*, **52**, 26–28.
- Pearson, B. S. (1969). The effects of Trasylol and aminocaproic acid in post-prostatectomy haemorrhage. *Br. J. Urol.*, **41**, 602.
- Pfaff, R., Ascherl, R., Blumel, G. *et al.* (1987). Local haemostasis of nephrostomy tract with fibrin adhesive sealing in percutaneous surgery. *Eur. Urol.*, **13**, 118–121.
- Salzman, E. (1990). Desmopressin and surgical hemostasis. *N Engl J Med.*, **322**, 1085.
- Schmutzler, R. and Furstenberg, H. (1966). The effect of E-aminocaproic acid and trasylol on fibrinolysis and blood loss after operations on the prostate. *Gen. Med. Mth.*, **11**, 390–396.
- Schultz, A. and Christiansen, L. A. (1985). Fibrin adhesive sealing of ureter after urethral stone surgery. *Eur. Urol.*, **11**, 267–268.
- Sharifi, R., Lee, M. and Ray, P. (1984). Local fibrinolysis in early post-TURP patients. In *The Third Congress of the International*

- Society of Urologic Endoscopy*, ed. Matouschek, E. Pp. 341–343. Karlsruhe Bua-Verlag Werner Steinbruck.
- Spehr, C.** (1986). Fibrin sealant in reconstruction of the infantile urethra. In *Fibrin Sealant in Operative Medicine, Gynaecology and Obstetrics-Urology*, ed. Schlag, G. and Redl, H. Volume 3. Pp. 136–140. Berlin, Heidelberg: Springer-Verlag.
- Sugawa, C., Fujita, Y., Ikeda, T. et al.** (1986). Endoscopic hemostasis of bleeding of the upper gastrointestinal tract by local injection of ninety-eight per cent dehydrated ethanol. *Surg Gynecol. Obstet.*, **162**, 159–163.
- Swinyard, E. A. and Pathak, M. A.** (1980). Surface acting drugs. In *The Pharmacological Basis of Therapeutics*, ed Goodman, L. S. and Gilman, A. Sixth edition. P. 955. New York Macmillan.
- Toft, A. D., Campbell, I. W. and Sawers, J. S. A.** (1984). *The Pharmacology of the Endocrine System*, ed Girwood, R. H. Twenty-fifth edition. Chapter 10, pp 375–376 London Bailliere Tindall.
- Towler, J. M. and Valerio, D.** (1978). Dicyclic in transurethral resection of the prostate. *Br. J. Urol.*, **50**, 547–550.
- Uriesberger, H. and Henning, K.** (1986). Transperitoneal and vaginal closure of vesicovaginal fistulae with fibrin sealant. In *Fibrin Sealant in Operative Medicine, Gynaecology and Obstetrics-Urology*, ed. Schlag, G. and Redl, H. Volume 3. Pp. 143–146. Berlin, Heidelberg: Springer-Verlag.
- Vecsey, D.** (1986). The use of fibrin sealant in urology. In *Fibrin Sealant in Medicine, Gynaecology and Obstetrics-Urology*, ed. Schlag, G. and Redl, H. Volume 3. Pp. 120–124. Berlin, Heidelberg: Springer-Verlag.
- Watson, A. M., Deane, A. M., Doyle, P. T. et al.** (1990). Identifiable factors in post-prostatectomy haemorrhage. the role of aspirin. *Br J Urol*, **66**, 85–87.
- Weintensfelder, W., Henning, K., Lexer, G. et al.** (1986). Fibrin sealant application in pelvic vein bleeding due to surgery in the small pelvis. In *Gynaecology and Obstetrics-Urology*, ed. Schlag, G. and Redl, H. Volume 3. Berlin, Heidelberg: Springer-Verlag.

The Authors

- T. P. Briggs, BSc, FRCS, Fresenius Research Fellow.
 C. Parker, FRCS, Registrar in Urology.
 K. Anson, FRCS, Research Fellow.
 R. A. Miller, MS, FRCS, Consultant Urologist.

Requests for reprints to: T. P. Briggs, Department of Urology and Minimally Invasive Surgery, Whittington Hospital, Highgate Hill, London N19 5NF.

Adult Wilms' Tumour: Review of 14 Patients

GRANT WILLIAMS, R. A. COLBECK and N. F. C. GOWING

Nephro-urology Unit, Harley Street Clinic; Department of Urology, Northwick Park Hospital; Department of Histopathology, Royal Marsden Hospital, London

Summary—Wilms' tumour, or nephroblastoma, is the commonest renal neoplasm found in children, but is rarely found in adults, the world literature recording only approximately 200 cases. Individual case reports continue to be published but only within the last 10 years have definitive treatment regimes been suggested. In order to determine the UK experience of adult Wilms' tumour, members of the British Association of Urological Surgeons were circulated with a questionnaire, and from 141 replies, 13 members reported 17 cases. Critical review of the original histology slides excluded 3 of these; the 14 remaining cases are described and their management discussed in the light of current recommended treatment.

Nephroblastoma (Wilms' tumour) is a malignant embryonic tumour of the kidney, which arises from the metanephric blastema. It is the commonest renal neoplasm in children and accounts for approximately 20% of all malignant tumours in this age group.

The first comprehensive account of the tumour was given by Wilms (1899), although a specimen existed in the Hunterian Museum and was described by Rance (1814) and Gairdner (1828) as "Fungus Haematodes of the Kidney".

The incidence of the tumour in adults is estimated at about 1% of all cases and about 200 cases have been described in the world literature to date (Roth *et al.*, 1984). At least 53 synonyms have been used to describe the tumour (Culp and Hartman, 1948). Babaian *et al.* (1980) reviewed the collected series of Wilms' tumours in adults which had appeared in the world literature since 1878 and determined that a total of only 167 cases had been reported. Because of this rarity, the exact incidence of the tumour is difficult to ascertain and the most effective form of treatment is unknown.

Patients and Methods

Sporadic reports of Wilms' tumour in adults continue to be published and it was the experience

of 1 of us (GW) in managing 2 patients within 7 years which prompted a survey of the members of BAUS to discover their collective experience, document the patients and determine if any patterns of treatment emerged. A questionnaire was circulated to all members asking whether they had ever operated on any individual over the age of 20 with a Wilms' tumour. Positive responders were asked for details of the patient's history and management and for slides of the original histology specimens. A total of 17 adults believed to have Wilms' tumours were reported by members of BAUS. In all of these cases the original histological sections were reviewed (NFCG). Of the 17 specimens reviewed, 3 did not meet the criteria for diagnosis of adult Wilms' tumour. One, in a female, was possibly "a bone seeking renal sarcoma of childhood" and the other 2, in females, were other anaplastic malignant neoplasms.

The remaining 14 specimens satisfied the histological criteria and are summarised in Table 1. All the neoplasms featured undifferentiated blastema as seen in childhood cases, composed of darkly staining, spheroidal, ovoid and fusiform cells with hyperchromatic nuclei and relatively scanty cytoplasm. Tubule formation was seen in 11 tumours and 2 displayed prominent glomeruli. In no specimen was differentiated mesenchymal tissue present, neither were heterologous tissues (*e.g.*,

Table 1 Summary of Principal Histological Features of 14 Patients with Adult Wilms' Tumour

Patient No.	Sex	Age	Stage	Principal histological features
1	F	36	I	Mixture of undifferentiated blastema and abundant tubules
2	F	30	I	Undifferentiated blastema with numerous tubules and progglomeruli, sections of lung also examined with metastases
3	F	22	I	Mainly undifferentiated blastema, with tubules and progglomeruli
4	M	45	I	Mixture of undifferentiated blastema and abundant tubules
5	M	28	IV	Undifferentiated, metastatic deposit in section of adrenal
6	M	28	II	Mainly undifferentiated but with some tubule formation
7	F	21	III	Mixture of undifferentiated blastema and abundant tubules
8	F	33	III	Undifferentiated blastema and moderate number of tubules
9	M	21	IV	Mainly undifferentiated but with some tubule formation
10	M	23	IV	Mainly undifferentiated but with some tubule formation
11	M	22	NK	Undifferentiated
12	M	NK	NK	Mixture of undifferentiated blastema, tubules and progglomeruli
13	F	26	NK	Undifferentiated
14	NK	20	NK	Predominantly undifferentiated but with tubule formation

NK = Not known

striated muscle, cartilage or bone) found (Figs 1, 2 and 3).

Some of the confusion in reporting arises from the problems of histological interpretation of renal tumours in adults. Kilton *et al.* (1980) described criteria for the diagnosis of adult Wilms' tumour. These are (1) a primary renal neoplasm, (2) primitive blastematous spindle or round cell component, (3) formation of abortive or embryonal

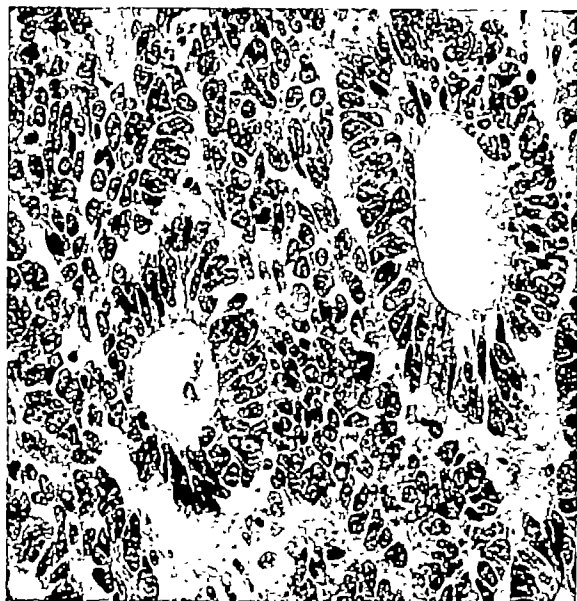


Fig. 1 Adult nephroblastoma showing tubule formation and intervening, undifferentiated spheroidal and fusiform cells. (H and E $\times 312$).

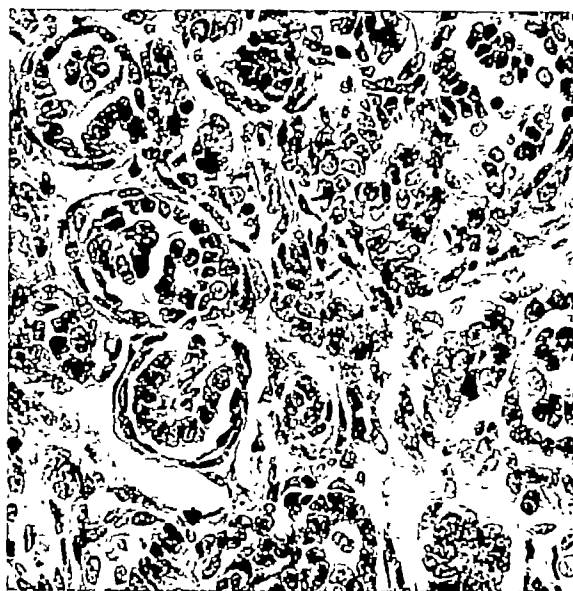


Fig. 2 Adult nephroblastoma featuring many tubules with intraluminal tufts: embryonic glomeruli or progglomeruli. (H and E $\times 312$)

tubular or glomeruloid structures, (4) no area of tumour diagnostic of renal carcinoma, (5) pictorial confirmation of histology and (6) age > 15 years.

Of 192 adult patients with Wilms' tumour reported up to 1980, 75% had unconvincing or absent photomicrographs or incomplete histological description (Kilton *et al.*, 1980).

Our 14 confirmed patients are summarised in Table 2 and their management and subsequent progress discussed in the light of current treatment

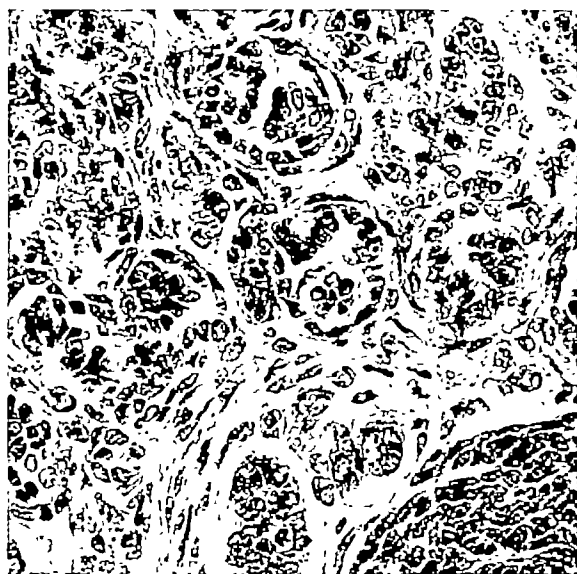


Fig. 3 Adult nephroblastoma showing proglomeruli, intervening undifferentiated spindle-shaped cells and a solid mass of undifferentiated tumour cells (in lower right corner of the field). (H and E $\times 312$).

regimes. In all, 10 patients have substantially complete records. Histology slides were available for the remaining 4, but not clinical details.

Results

A total of 10 cases of nephroblastoma are described in Table 1, and a further 4 poorly documented cases are noted. Only the 10 well documented cases are discussed. The youngest patient was aged 15 and the oldest 45 years, 5 were men and 5 were women.

The disease was staged according to the criteria of the National Wilms' Tumor Study (Breslow *et al.*, 1981).

At the time of initial diagnosis 9 patients underwent removal of the primary renal tumour. One patient, case 5, with an extensive renal tumour, was considered inoperable and treated with vincristine, doxorubicin hydrochloride and methotrexate on the erroneous diagnosis of lymphoma. After 5 months the mass had shrunk considerably and he had a second exploration and subsequent right nephrectomy. A further 4 patients received radiotherapy to the primary tumour site, 2 with stage I disease, 1 with stage II and 1 with stage III. Radiotherapy was given to 4 patients who developed metastatic disease—3 patients with pulmonary metastases and 1 patient with a local loin

recurrence. These 4 patients subsequently died of their disease.

Only 1 patient was managed without adjuvant radiotherapy or chemotherapy. The most frequently used chemotherapeutic agents for primary disease were vincristine (8 patients), doxorubicin hydrochloride (6 patients), actinomycin-D (5 patients) and cyclophosphamide (4 patients). Less commonly used were prednisolone (1 patient) and methotrexate (1 patient).

In the treatment of secondary deposits, the following agents were used: cisplatin (3), etoposide (2), doxorubicin hydrochloride (3), actinomycin-D (2), cyclophosphamide (1), 5-fluorouracil (1) and prednisolone (1). Of the 4 patients with stage I disease, only 2 received chemotherapy as a primary treatment.

Discussion

This review was undertaken because there appears to be no agreed protocol for the treatment of adult Wilms' tumour.

Wilms' tumour arises from the totipotential cells of the metanephrogenic blastema, and although commonest in children, has presented in all age groups, up to the age of 82. The degree of differentiation of the tumour has been found to correlate with survival, and 2 categories of histology, favourable and unfavourable, have been proposed (Beckwith and Palmer, 1978). The metastatic sites of these differ, the favourable spreading to the lungs and the unfavourable to the bones. In this series, the histology was not assigned to 1 or other group in the majority of cases.

It is difficult to make comparisons in a small series of 10 patients, when there is no multicentre national study with strict treatment criteria. However, a broad picture emerges of the probable fate of patients within each stage, and the effect of treatment on the progress of their disease. The treatment of childhood Wilms' tumour has made dramatic improvements since the 1920s, when only 5% were expected to survive 2 years. Advances in surgical techniques improved the 2-year survival rate to 20%. The addition of renal tumour bed irradiation brought another improvement in survival to 40%. The addition in the 1960s of adjuvant chemotherapy has resulted in the current cure rate of >80% (D'Angio *et al.*, 1976). However, the results of the treatment of adult Wilms' tumour have not been as successful. Byrd *et al.* (1982) described 31 adults who were reported to the National Wilms' Tumor Study from 1968 to 1979.

Table 2 Details of Treatment and Survival of Patients with Adult Wilms' Tumour

Case	Age	Sex	Presentation	Stage	Surgery	Radiotherapy	Chemotherapy	Outcome
1	36	F	L loin pain	I	Transabdominal nephrectomy	4250 cGy renal bed	Vincristine Doxorubicin Cyclophosphamide Actinomycin-D	Alive 33 months
2	30	F	L loin pain L loin mass	I	Transabdominal nephrectomy L. lower lobe lobectomy at 7 years for metastasis	—	Vincristine Doxorubicin Actinomycin-D	Alive 17 years
3	15	F	Haematuria	I	L. nephrectomy R partial nephrectomy	—	Details unknown	Alive 9 years
4	45	F	Painless haematuria	I	R. nephrectomy	3000 cGy to renal bed 2000 cGy to lung	Vincristine Actinomycin-D Doxorubicin	Died 6½ years
5	28	M	Loin mass Haematuria	IV	R nephrectomy following chemotherapy	—	Vincristine Doxorubicin Methotrexate Prednisolone	Died 21 months
6	28	M	Painless haematuria	II	L. nephrectomy	4000 cGy to renal bed	Vincristine Actinomycin-D	Alive 5 years
7	21	F	Haematuria	III	Transabdominal nephrectomy	2000 cGy to lung	Vincristine Actinomycin-D Cyclophosphamide Cisplatin	Died 8 months
8	33	F	L loin pain and UTI	III	L lower polar hemi-nephrectomy Completion nephrectomy at 2 months	4100 cGy to renal bed 2400 cGy to lung 5170 cGy to local recurrence	Vincristine Doxorubicin	Died 2 years
9	21	M	Haematuria	IV	L. nephrectomy Open lung biopsy	—	Vincristine Doxorubicin Cyclophosphamide Bleomycin Etoposide Cisplatin Methotrexate 5-Fluorouracil	Died 7 months abroad
10	23	M	Loin pain Haematuria	IV	L nephrectomy	Abdominal and pulmonary irradiation	Vincristine Doxorubicin Actinomycin-D Cyclophosphamide Etoposide Cisplatin	Died at 4 months
11	22	M	NK	NK	NK	NK	NK	NK
12	NK	M	NK	NK	NK	NK	NK	Died aged 21
13	26	F	NK	NK	NK	NK	NK	NK
14	20	F	NK	NK	NK	NK	NK	NK

NK = Not known

Their 3-year survival rate was 24%: 48% for stages I and II, and 11% for stage IV disease. This contrasts with children's survival rates of 74%, 87% and 53% respectively. In our series, 100% of stage I patients were alive at 2 years, and 80% of stage I and II at 3 years. Conversely, the stage IV patients did very poorly, none surviving 3 years, and the longest surviving living only 7 months after diagnosis.

Adult Wilms' tumour should be a potentially curable disease. The major problem confronting a surgeon faced with a patient over 16 years of age with a nephroblastoma is the lack of any defined treatment protocol, due principally to the rarity of the disease. In children, long experience and centralised studies have led to well defined treatment protocols for the various stages. The fundamental treatment is trans-abdominal nephrectomy with node biopsy and assessment of the opposite kidney to exclude bilateral disease. During the 1960s actinomycin-D was found to be an effective drug and the second National Wilms' Tumor Study reported that a combination of vincristine and actinomycin-D was superior to either agent used singly (D'Angio *et al.*, 1976). For late disease, a 3 or 4 drug combination is used, adding doxorubicin hydrochloride and cyclophosphamide (Dunger *et al.*, 1981).

The United Kingdom Children's Cancer Study Group trial protocol recommended division into favourable and unfavourable histological groups. The favourable groups all underwent surgery, followed by vincristine for 6 months in stage I; vincristine, actinomycin-D and radiotherapy in stage II and vincristine, actinomycin-D, doxorubicin hydrochloride and radiotherapy in stage III disease. Operable but unfavourable disease of all stages, and stage IV favourable disease receive surgery and 4-agent chemotherapy: actinomycin-D, doxorubicin hydrochloride, vincristine and cyclophosphamide (DAVE), followed by a second-look laparotomy at 20 weeks, and possibly subsequent radiotherapy.

For inoperable tumours, DAVE was given with radiotherapy to the lung or abdomen, and a second-look laparotomy with continuing chemotherapy if tumour was still present. A number of authors have made recommendations for the treatment of adult disease based either on their own experiences, or reviews of a number of cases. Babaian *et al.* (1980) described 3 cases and treated them according to the National Wilms' Tumor Protocol, proposing for stage I disease nephrectomy followed by vincristine and actinomycin-D; stage II and III receive local

radiotherapy in addition, and stage IV patients receive the same treatment plus irradiation of metastatic deposits. Kilton *et al.* (1980) took into account their own analysis of 35 patients and the National Wilms' Tumor Study, and suggested a protocol for all stages consisting of an operation for diagnosis, debulking and definition of the tumour bed for irradiation. All patients received 3500 to 4000 cGy post-operatively with added whole lung irradiation if pulmonary secondaries were present, with adjuvant chemotherapy as for childhood Wilms' tumour using vincristine and actinomycin-D. They felt that radiotherapy was of demonstrable value, either obtaining a response in metastatic disease or converting inoperable primary disease to operable.

Byrd *et al.* (1982) reviewed 31 adults reported to the National Wilms' Tumor Study. They concluded that aggressive multimodal therapy be used in all stages of the disease, using surgery, post-operative irradiation and multi-agent chemotherapy, including at least actinomycin-D, vincristine and doxorubicin hydrochloride. Roth *et al.* (1984) reported 2 patients, 1 with stage I disease treated by excision and actinomycin-D and vincristine who survived disease-free for 3 years and 1 with stage II disease, treated with tumour bed irradiation and vincristine, doxorubicin hydrochloride and actinomycin-D. They reinforced the concept of aggressive treatment with combination chemotherapy and irradiation. Advanced disease in 2 patients was reported by Hagiwara *et al.* (1982) and illustrated the role of surgery in recurrent disease. One patient presented with stage I disease and underwent nephrectomy and tumour bed irradiation only. Two years later she developed a solitary recurrence in the liver and following combination chemotherapy with actinomycin-D and vincristine, and 6000 cGy irradiation, the metastasis was resected by an extended right hepatic lobectomy. She remained disease-free 4 years later. The other patient had advanced disease including venous extension of tumour thrombus to the right atrium, with pulmonary metastases. The primary tumour was removed together with the thrombus and the metastases were successfully treated with combination chemotherapy. This report underlines the fact that late metastatic disease must be anticipated—in our series a pulmonary metastasis appeared after 7 years—and treated aggressively, by resection if necessary, combined with chemotherapy.

What conclusions about adult Wilms' tumours may be drawn from this series?

The first is that the tumour is rare, and most

surgeons will be unlikely to encounter 1 in a lifetime of practice. If they do, it is likely to be in a young adult, in their mid-twenties, who presents with the classical signs of a renal neoplasm. Imaging of any modality is unlikely to provide any diagnostic features. Similarly, angiographic features are not pathognomonic and tumours may be hypovascular, avascular or show neovascularity (Meng and Elkin, 1969). Immediate screening for metastatic disease should include CT scanning of the lungs and abdomen, and an isotope scan.

The discovery of metastatic disease should not prevent exploration and attempted removal of the primary tumour. If the primary tumour is initially inoperable, then following chemotherapy, a second-look laparotomy is worth consideration.

Operation should establish the diagnosis, debulk the tumour and define the tumour bed for subsequent irradiation. Formerly, post-operative abdominal irradiation was used, but is of dubious value. Similarly, whole lung irradiation has not been shown to be valuable.

Chemotherapy should be used for all patients, including vincristine, actinomycin-D and doxorubicin hydrochloride, on the basis that these drugs are of proven benefit in childhood tumours. Since the prognosis is generally poorer in adults, combination chemotherapy offers the best hope of cure if used in all stages in the adult.

Our experience also suggests that solitary metastases are worth treating aggressively by excisional surgery wherever feasible and that local recurrence tends to be associated with a poor prognosis.

Acknowledgements

We thank all of the surgeons who replied to the questionnaire and, in particular, the following surgeons, pathologists and radiotherapists for allowing us to include their patients in this study and for providing relevant information: I. Appleyard, R. H. Begent, A. R. Blacklock, Professor J. Blandy, E. C. Edwards, A. Ford, R. Gray, N. A. Green, N. Howard, M. A. Hughes, P. Jarrett, A. McEwan, R. T. Oliver, R. Pointon, D. Richards, J. Rode, K. Shuttleworth, E. Tinsley, R. Williams and P. Worth.

References

- Babalan, R. J., Skinner, D. G. and Walsman, J. (1980) Wilms' tumour in the adult patient: diagnosis, management, and review of the world medical literature. *Cancer*, **45**, 1713-1719.
- Beckwith, J. B. and Palmer, N. F. (1978). Histopathology and prognosis of Wilms' tumor. Results from the First National Wilms' Tumor Study. *Cancer*, **41**, 1937-1948.
- Breslow, N. E., Palmer, N. F., Hill, L. R. *et al.* (1981). Wilms' tumor: prognostic factors for patients without metastases at diagnosis: results from the First National Wilms' Tumor Study. *Cancer*, **47**, 2302-2311.
- Byrd, R. L., Evans, A. E. and D'Angio, G. J. (1982). Adult Wilms' tumor: effect of combined therapy on survival. *J. Urol.*, **127**, 648-651.
- Culp, O. S. and Hartman, F. W. (1948). Mesoblastic nephroma in adults: a clinico-pathologic study of Wilms' tumor and related renal neoplasms. *J. Urol.*, **60**, 552-576.
- D'Angio, G. J., Evans, A., Breslow, N. *et al.* (1976). The treatment of Wilms' tumor: results of the Second National Wilms' Tumor Study. *Cancer*, **38**, 633-646.
- Dunger, D. B., Malpas, J. S., Graham-Pole, J. R. *et al.* (1981). The use of four-drug combination chemotherapy (DAVE) in the treatment of advanced Wilms' tumour. *Cancer Chemother Pharmacol*, **5**, 211-215.
- Gairdner, E. (1828). Fungus haematodes of the kidney. *Edin. Med. Surg. J.*, **29**, 312-315.
- Hagiwara, M., Tachibana, M., Jitsukawa, S. *et al.* (1982). Multimodal treatment of advanced Wilms' tumor. *J. Urol.*, **127**, 535-538.
- Kilton, L., Matthews, M. J. and Cohen, M. H. (1980). Adult Wilms' tumor: a report of prolonged survival and review of literature. *J. Urol.*, **124**, 1-5.
- Meng, C. and Elkin, M. (1969). Angiography manifestations of Wilms' tumor. *Am. J. Roentgenol.*, **105**, 95-104.
- Rance, T. F. (1814). Case of fungus haematodes of the kidney. *Med Phys J*, **32**, 19-25.
- Roth, D. R., Wright, J., Cawood, C. D. Jr *et al.* (1984). Neophroblastoma in adults. *J. Urol.*, **132**, 108-110.
- Wilms, M. (1899) *Die Mischgeschwulste der Niere* Leipzig, Georgi.

The Authors

- R. A. Colbeck, BSc, FRCS, Research Registrar, Department of Urology, Northwick Park Hospital.
- Grant Williams, MS, MSc, FRCS, Consultant Urologist, Harley Street Clinic.
- N. F. C. Gowing, MD, FRCPath, Emeritus Professor of Histopathology, Royal Marsden Hospital.

Requests for reprints to: Grant Williams, Nephro-urology Unit, Harley Street Clinic, London W1N 4BJ

Acquired Cystic Disease of the Kidney and Renal Carcinoma in Haemodialysis Patients: Ultrasonographic Evaluation

I. SASAGAWA, Y. TERASAWA, K. IMAI, H. SEKINO and H. TAKAHASHI

Kidney Centre and Department of Internal Medicine, Shakai-Hoken Hospital; Department of Internal Medicine, Kohjinkai Hospital, Sendai, Japan

Summary—Ultrasonography was performed in 661 dialysis patients and acquired cystic disease of the kidney was found in 156 (125 men and 31 women). A higher incidence of cystic disease was found in males. There was no significant difference between the patients with and those without acquired cystic disease in terms of average age, but the duration of haemodialysis in those with acquired cystic disease was significantly longer. There was an increased incidence of cystic disease in patients with glomerulonephritis and the duration of haemodialysis in these patients was significantly longer. This suggests that the increased incidence of acquired cystic disease of the kidneys in the patients with glomerulonephritis is simply related to the longer duration of treatment. Twelve patients with renal carcinoma were found in this study. The average age at diagnosis of renal carcinoma was not significantly different between the patients with and those without acquired cystic disease, but the duration of dialysis was significantly longer in renal carcinoma patients with acquired cystic disease. The incidence of renal carcinoma in dialysis patients with acquired cystic disease was 3.85% and in those without it was 1.19%. These rates are considerably higher than those found in the general population and indicate that the risk of renal carcinoma is higher in dialysis patients both with and without acquired cystic disease.

Since acquired cystic disease of the kidney (ACDK) was first defined by Dunnill *et al.* (1977), a substantial number of studies have been carried out on cystic changes in the kidneys of haemodialysis patients (Ishikawa *et al.*, 1980; Kutcher *et al.*, 1983; Narashimhan *et al.*, 1986). Acquired cystic disease of the kidney is now well recognised and its relationship with renal carcinoma has been emphasised by Ishikawa and Shinoda (1983) and Basile *et al.* (1988). However, most patients with this condition have no clinical symptoms. Periodic examination of the kidneys of haemodialysis patients is necessary for the early detection of renal carcinoma and the efficacy of ultrasonography in this respect has been reported by Terasawa *et al.* (1990). In the present study, we examined the

kidneys of haemodialysis patients by means of ultrasonography, and we discuss the prevalence of acquired cystic disease and renal carcinoma in dialysis patients.

Patients and Methods

The study group comprised 661 patients with end-stage renal disease of various causes. They included 393 males (59.5%) and 268 females (40.5%) with an age range of 15 to 83 years (median 54). All patients had been treated with haemodialysis for 1 to 225 months (median 75). The mean duration of haemodialysis in males and females was 79 months and 76 months respectively. Patients with polycystic kidneys and renal tuberculosis were excluded from the study.

Patients were examined with the Toshiba SSA-90A ultrasound machine using either a linear type

3.5 MHz probe, a sector type 3.75 MHz probe, or a convex type 3.75 MHz probe. Scans were performed in cross-section, longitudinal, coronal and, if necessary, oblique planes from anterior and posterior regions. Acquired cystic disease of the kidney was defined as the presence of a number of cysts in each kidney.

Results

As shown in Table 1, acquired cystic disease of the kidney was found in 156 of the 661 dialysis patients (23.6%). The commonest cause of renal failure in patients with ACDK was glomerulonephritis (78.9%). In patients without ACDK, the 2 main causes were glomerulonephritis (58.6%) and diabetes mellitus (17.4%) (Table 2). There was an increased incidence of cystic disease in patients with glomerulonephritis compared with the other groups ($P < 0.001$) and the duration of haemodialysis was significantly longer ($P < 0.001$) (Table 3).

Table 1 Clinical Characteristics of Patients with and without Acquired Cystic Disease of the Kidney (ACDK)

	No. of patients	Age (years)	Duration of dialysis (months)
ACDK (+)	156	50 ± 12	126 ± 52*
ACDK (-)	565	55 ± 15	59 ± 51

Each value represents mean ± SD.

* $P < 0.001$: compared to group without ACDK.

Table 2 Causes of Renal Failure in Dialysis Patients with and without Acquired Cystic Disease of the Kidney (ACDK)

Causes of renal failure	ACDK (+)	ACDK (-)
	No. (%)	No (%)
Glomerulonephritis	123* (78.9)	296 (58.6)
Diabetes mellitus	3 (1.9)	88 (17.4)
Toxaemia of pregnancy	2 (1.3)	21 (4.2)
Nephrotic syndrome	—	9 (1.8)
Chronic pyelonephritis	4 (2.6)	8 (1.6)
Systemic lupus erythematosus	2 (1.3)	6 (1.2)
Chronic obstructive uropathy	1 (0.6)	5 (1.0)
Others	18 (11.5)	28 (5.5)
Unknown	3 (1.9)	44 (8.7)
Total	156 (100.0)	505 (100.0)

* $P < 0.001$: compared to dialysis patients with other causes of renal failure.

Table 3 Duration of Haemodialysis in Patients with and without Glomerulonephritis

Cause of renal failure	ACDK (+)	ACDK (-)
Glomerulonephritis	n = 123 135 ± 45*† months n = 33	n = 296 72 ± 52* months n = 209
Non-glomerulonephritis	107 ± 56†	43 ± 43

Each value represents mean ± SD.

* $P < 0.001$: compared to patients without glomerulonephritis

† $P < 0.001$: compared to patients without ACDK.

There was no significant difference in age between dialysis patients with and without acquired cystic disease, but the duration of dialysis in those with ACDK was significantly longer ($P < 0.001$) (Table 1). The group of 156 patients with acquired cystic disease included 125 males (80.1%) and 31 females (19.9%). There was no difference in duration of dialysis between males and females, but the males had a significantly higher incidence of cystic disease ($P < 0.001$).

Twelve patients with renal carcinoma (1.82%) were detected in this study (Figs 1 and 2); they comprised 10 males (83.3%) and 2 females (16.7%) (Table 4). The incidence of renal carcinoma was significantly higher in dialysis patients with ACDK than in those without the disease ($P < 0.05$). Glomerulonephritis was the cause of renal failure



Fig. 1 Longitudinal ultrasonogram of left kidney shows an inhomogeneous solid mass in the upper portion (arrow).



Fig. 2 Longitudinal ultrasonogram of the left kidney reveals numerous small cysts in both cortex and medulla. A hyperechoic mass without posterior echo enhancement is seen in a cyst (arrow)

in all renal carcinoma patients with ACDK and in 4 of the 6 without ACDK. As shown in Table 5, the average age at diagnosis of renal carcinoma was not significantly different between the 2 groups. However, there was a significant difference between the 2 groups in respect of the time from initiation of dialysis to diagnosis of renal carcinoma ($P < 0.001$).

Discussion

Acquired cystic disease of the kidney is the term used to describe the occurrence of numerous small cysts in bilateral contracted kidneys of dialysis patients. The reported incidence ranges from 10 to 95% (Grantham and Levine, 1985; Narashimhan *et al.*, 1986). Cystic changes in the kidneys were

Table 5 Clinical Characteristics of Renal Carcinoma in Dialysis Patients with and without Acquired Cystic Disease of the Kidney (ACDK)

	No. of dialysis patients	No. of patients with renal carcinoma	Age (years)	Duration of dialysis (months)
ACDK (+)	156	6*	50 ± 8	158 ± 30†
ACDK (−)	505	6	53 ± 11	43 ± 35

Each value represents mean ± SD.

* $P < 0.05$: compared to group without ACDK.

† $P < 0.001$: compared to group without ACDK.

found in 23.6% of our patients. The development of ACDK appears to be related to the duration of haemodialysis (Ishikawa *et al.*, 1980). In the present study, the duration of haemodialysis was significantly longer in patients with ACDK than in those without it. Renal transplantation causes the disappearance of acquired cysts and a marked decrease in the size of the native kidneys. Reinstitution of haemodialysis is associated with the reappearance of the cysts together with renal enlargement (Ishikawa *et al.*, 1983). Uraemic metabolites or haemodialysis itself may be responsible for the acquired cystic changes. Our study has shown an increased incidence of cystic disease in patients with glomerulonephritis when compared with the other groups, but the duration of dialysis in patients with glomerulonephritis was significantly longer. This implies that the increased incidence of acquired cystic disease in patients with glomerulonephritis is simply related to the longer duration of therapy. Sex differences in acquired cystic disease of the kidney were observed in this study. According to Ishikawa *et al.* (1985), long-term follow-up showed that the size of the kidneys and the number of acquired cysts were greater in males than in females. Sex-related endogenous substances are thought to play a part in the pathogenesis of acquired cystic disease.

Several reports have dealt with the increased incidence of cystic changes and neoplasms in the kidneys of dialysis patients (Ishikawa and Shinoda, 1983; Basile *et al.*, 1988). In the present study, renal carcinomas were detected in 12 of 661 dialysis patients (1.82%), an incidence that is more than 30-fold above that in the general population (Terasawa *et al.*, 1990). Renal carcinoma is approximately 20 times as common among dialysis patients without acquired cystic disease and over 60 times as common in the dialysis population with the disease.

Table 4 Sex Distribution of Patients with Acquired Cystic Disease of the Kidney (ACDK) and Renal Carcinoma

Sex	No of patients (%)	ACDK	Renal carcinoma
		No. (%)	No. (%)
Male	393 (59.5)	125* (80.1)	10 (83.3)
Female	268 (40.5)	31 (19.9)	2 (16.7)
Total	661 (100.0)	156 (100.0)	12 (100.0)

* $P < 0.001$: compared to female.

Hughson *et al.* (1980) reported a statistically significant relationship between the occurrence of multiple cysts and neoplasms. In an animal model, cystic disease and tumours in the kidney were provoked by streptozotocin (Lee *et al.*, 1974). Also, the administration of cisplatin resulted in cysts and tumour formation in the kidney (Dobyan *et al.*, 1981). This suggests that ACDK is a pre-malignant state.

According to Ishikawa and Shinoda (1983), there were 2 groups of renal carcinomas. The tumours found after relatively short periods of dialysis occurred in patients over 50 years of age and were accompanied by fewer cystic formations. In contrast, carcinomas in patients less than 50 years of age were found after longer periods of dialysis in kidneys showing more pronounced cystic changes. Although the average age at diagnosis of renal tumours was not significantly different between dialysis patients with and those without ACDK, patients with the disease had undergone dialysis for a longer period of time. These findings indicate that patients with end-stage renal disease have an increased risk of developing renal carcinoma that is related to the duration of dialysis and to the presence of acquired cystic disease. However, the incidence of renal carcinoma was higher both in those with and without acquired cystic disease. Regular follow-up with ultrasonography should be considered in dialysis patients with and without cystic disease.

References

- Basile, J. J., McCullough, D. L., Harrison, L. H. *et al.* (1988). End stage renal disease associated with acquired cystic disease and neoplasia. *J. Urol.*, **140**, 938–943.
- Dobyan, D. C., Hill, D., Lewis, T. *et al.* (1981). Cyst formation in rat kidney induced by cis-platinum administration. *Lab Invest.*, **45**, 260.
- Dumill, M. S., Millard, P. R. and Oliver, D. (1977). Acquired cystic disease of the kidneys. A hazard of long-term intermittent maintenance hemodialysis. *J. Clin. Pathol.*, **30**, 868–877.
- Grantham, J. J. and Levine, E. (1985). Acquired cystic disease. Replacing one kidney disease with another. *Kidney Int.*, **28**, 99–105.
- Hughson, M. D., Hennigar, G. R. and McManns, J. F. A. (1980). Atypical cysts, acquired renal cystic disease, and renal cell tumours in end stage dialysis kidneys. *Lab. Invest.*, **42**, 475–480.
- Ishikawa, I., Onouchi, Z., Saito, Y. *et al.* (1985). Sex differences in acquired cystic disease of the kidney on long-term dialysis. *Nephron*, **39**, 336–340.
- Ishikawa, I., Saito, Y., Onouchi, Z. *et al.* (1980). Development of acquired cystic disease and adenocarcinoma of the kidney in glomerulonephritic chronic hemodialysis patients. *Clin. Nephrol.*, **14**, 1–6.
- Ishikawa, I. and Shinoda, A. (1983). Renal adenocarcinoma with or without acquired cysts in chronic hemodialysis patients. *Clin. Nephrol.*, **20**, 321–322.
- Ishikawa, I., Yuri, T., Kitada, H. *et al.* (1983). Regression of acquired cystic disease of the kidney after successful renal transplantation. *Am. J. Nephrol.*, **3**, 310–314.
- Kutcher, R., Amodio, J. B. and Rosenblatt, R. (1983). Uremic renal cystic disease. Value of sonographic screening. *Radiology*, **147**, 833–835.
- Lee, C. S., Mauer, S. M., Brown, D. M. *et al.* (1974). Renal transplantation in diabetes mellitus in rats. *J. Exp. Med.*, **139**, 793–800.
- Narashimhan, N., Golper, T. A., Wolfson, M. *et al.* (1986). Clinical characteristics and diagnostic considerations in acquired renal cystic disease. *Kidney Int.*, **30**, 748–752.
- Terasawa, Y., Fukuda, Y., Kato, M. *et al.* (1990). Study on small renal cell carcinoma diagnosed by ultrasonography. *Jpn. J. Urol.*, **81**, 1232–1239.

The Authors

I. Sasagawa, MD, Urologist
Y Terasawa, MD, Physician.
K. Imai, MD, Physician.
H Sekino, MD, Urologist.
H Takahashi, MD, Urologist.

Requests for reprints to: I. Sasagawa, Department of Urology, School of Medicine, Yamagata University, 2-2-2 Iidanishi, Yamagata-shi, Yamagata 990-23, Japan.

Agglomeration of Calcium Oxalate Monohydrate in Synthetic Urine

F. GRASES, L. MASÁROVÁ, O. SÖHNEL and A. COSTA-BAUZÁ

Department of Chemistry, University of the Balearic Islands, Palma de Mallorca, Spain

Summary—The development of agglomerated particles of calcium oxalate monohydrate (COM) on the semi-batch precipitation from a synthetic urine carried out at physiological conditions (37°C, pH=5.5) was studied by optical and electron scanning microscopy. COM agglomerates develop by primary and secondary agglomeration proceeding simultaneously; the latter mechanism is, however, less important than the former. Citrate ions modify slightly the COM crystal shape and inhibit primary agglomeration. Mucin particles serve as a substrate for preferential formation (nucleation) of new COM crystals. The structure of formed agglomerates closely resembles that of a certain type of COM renal calculi. A combination of primary agglomeration of crystals forming stones and nucleation of new crystals on a mucoprotein layer partially covering their surface constitutes the possible mechanism of such stone development. Experimental data support this mechanism.

The agglomeration of calcium oxalate monohydrate (COM) crystals is recognised as an important step in renal stone development (Robertson *et al.*, 1976, 1981; Schneider, 1985). The mechanism governing this process, however, still remains to be clarified.

The only mechanism of agglomeration that has been described quantitatively proceeds through crystal-crystal collisions induced by hydrodynamic forces in a liquid medium containing crystals (von Smoluchowski, 1918). This process, usually termed secondary agglomeration, cannot represent a significant mechanism of renal calculi development due to conditions prevailing in the kidney (Finlayson, 1978).

Recent experimental results of the semi-batch precipitation of COM indicated primary agglomeration as a possible mechanism for the development of calculi (Grases *et al.*, 1992; Millan *et al.*, 1992). Primary agglomeration represents a sort of crystal mal-growth that takes place on the surface and/or tips of already developed crystals, the so-called parent crystals (Buckley, 1951; Jones, 1989). This process results in concretions consisting of

intergrown crystals with a complex crystal arrangement that closely resembles the structure of certain types of COM renal calculi. Primary agglomeration of COM crystals forming a stone, in combination with the effect of mucoproteins adsorbed on the exposed calculus surface, appear to constitute a development mechanism for certain types of COM renal calculi (Grases *et al.*, 1992).

This conclusion was based mainly on results achieved following the semi-batch precipitation of pure calcium chloride and sodium oxalate solutions, *i.e.* on experiments carried out under conditions not fully consistent with physiological ones. Therefore, further experiments in a urine-like liquor were needed in order to corroborate the feasibility of this mechanism of COM calculi development.

We present the results of the semi-batch precipitation of COM carried out *in vitro* under conditions as close as possible to those expected *in vivo*.

Materials and Methods

A semi-batch precipitation was carried out in a magnetically stirred unbaffled beaker of 1 L capacity immersed in a constant temperature water bath with the temperature adjusted to 37°C; 50 ml of a

solution saturated with respect to calcium oxalate (see below) were placed in the beaker and agitated until 37°C was reached. Two solutions, A and B, were then introduced simultaneously at the combined rate of 200 ml/h (*i.e.* 100 ml/h for each solution) on to a liquid surface through separate inlets. The inlets were situated on opposite sides of the reaction beaker. The samples of reaction mixture withdrawn throughout each run were immediately observed under an optical microscope and solid phase was viewed by an electron scanning microscope.

One litre of solution A contained 11.02 g $\text{Na}_2\text{SO}_4 \cdot 10 \text{H}_2\text{O}$, 1.46 g $\text{MgSO}_4 \cdot 7 \text{H}_2\text{O}$, 4.64 g NH_4Cl , 12.13 g KCl and 1.413 g $\text{CaCl}_2 \cdot 3.5 \text{H}_2\text{O}$. Solution B contained 6.80 g $\text{NaH}_2\text{PO}_4 \cdot 2 \text{H}_2\text{O}$, 2.18 g $\text{Na}_2\text{HPO}_4 \cdot 12 \text{H}_2\text{O}$, 13.05 g NaCl , 0.287 g $\text{Na}_2\text{C}_2\text{O}_4$ and, unless stated otherwise, 1.16 g $\text{Na}_3\text{C}_6\text{H}_5\text{O}_7 \cdot 2 \text{H}_2\text{O}$ per litre. These substances of analytical grade purity were dissolved in distilled water. Some experiments were performed with solutions containing double the quantity of calcium chloride and sodium oxalate indicated above, *i.e.* 2.82 g $\text{CaCl}_2 \cdot 3.5 \text{H}_2\text{O}$ and 0.537 g $\text{Na}_2\text{C}_2\text{O}_4$ respectively. A series of experiments in the presence of mucin (from porcine stomach (Sigma Chem. Co., USA) was also performed. In this case 0.2 g/l of mucin were dissolved in solution A, whereas the composition of solution B was not changed. The pH of both solutions was adjusted prior to each

experiment to the value of 5.5 by adding HCl and NaOH , as appropriate.

The saturated solution charged into the reaction beaker at the beginning of each experiment was prepared by filtering the suspension resulting from the semi-batch precipitation carried out under conditions of a respective experiment for approximately 5 h.

Results

Individual crystals formed in the reaction mixture always behaved in a manner typical of calcium oxalate monohydrate.

The development of agglomerates during the semi-batch precipitation of calcium oxalate was, in principle, similar for all reaction conditions examined. Tiny and often individual crystals were detected in the system by an optical microscope within 10 to 20 min after the onset of introducing reactant solutions into the reactor (Fig. 1A). On continuing such introduction, individual crystals gradually developed into agglomerates, "loose" at the beginning and compact later (Fig. 1B). The size of the agglomerates increased with progressing precipitation.

The presence of citrate suppressed agglomeration to some extent. The rate of agglomerate development was slower and the average size reached



Fig. 1 Development of COM agglomerates in a synthetic urine containing no citrate. ($\times 400$). (A) Initial COM crystals. (B) Compact agglomerates.

within a certain time was smaller than at precipitation of solutions containing no citrate.

The presence of mucin significantly altered the course of agglomerate formation when compared with precipitation carried out without mucin. COM crystals were preferentially formed on mucin particles and the nucleation in the solution bulk was substantially suppressed (Fig. 2A). The first COM crystals could be observed on the surface of amorphous mucin particles after a certain time had elapsed. With progressing precipitation, the mucin particles became completely "surrounded" by COM crystals and thereafter could not be distinguished (Fig. 2B). The size of agglomerates increased during further precipitation, but the increase was less than in the system containing no mucin particles. Citrate present in the mucin-containing system, even when 3 times as high as in the standard solution B, did not exert any significant influence on the agglomeration process. Agglomerates formed on mucin particles were of the same character as COM agglomerates formed without mucin.

Details of agglomerate structure during development were revealed by electron scanning microscopy.

At the start of precipitation, COM formed individual elongated crystals and small intergrown composites of different shapes (Fig. 3A). "Loose" agglomerates consisting mainly of plate-like inter-

grown crystals developed from these crystals at early stages of precipitation (Fig. 3B). Compact agglomerates, around 50 μm in diameter, which appeared at later stages of precipitation, were composed of large interconnected crystals and a number of smaller plate-like crystals. Small crystals were mostly intergrown and originated both on the surface and tips of the parent crystals; in the latter case typical "rosette" structures were formed (Fig. 3C).

When citrate ions are present in a precipitating system the shape of both initial and agglomerate-forming crystals is changed when compared with the situation without citrate (Fig. 3D). Intergrown crystals forming an agglomerate are apparently less clearly defined and the extensive occurrence of new small crystals on the parent crystals is almost absent.

If mucin is present in a synthetic urine, small and unconnected COM crystals form first on their surface (Fig. 4A). These particles later become completely covered by a "crust" of intergrown plate-like COM crystals, many of them clearly originating on the parent crystals. Small spherical "sub-formations" consisting of plates arranged in star-like structures can be observed on the surface of large agglomerates (Fig. 4B). Such formations were not observed on agglomerates formed without mucin. Citrate ions do not markedly influence the shape, size and arrangement of COM crystals in

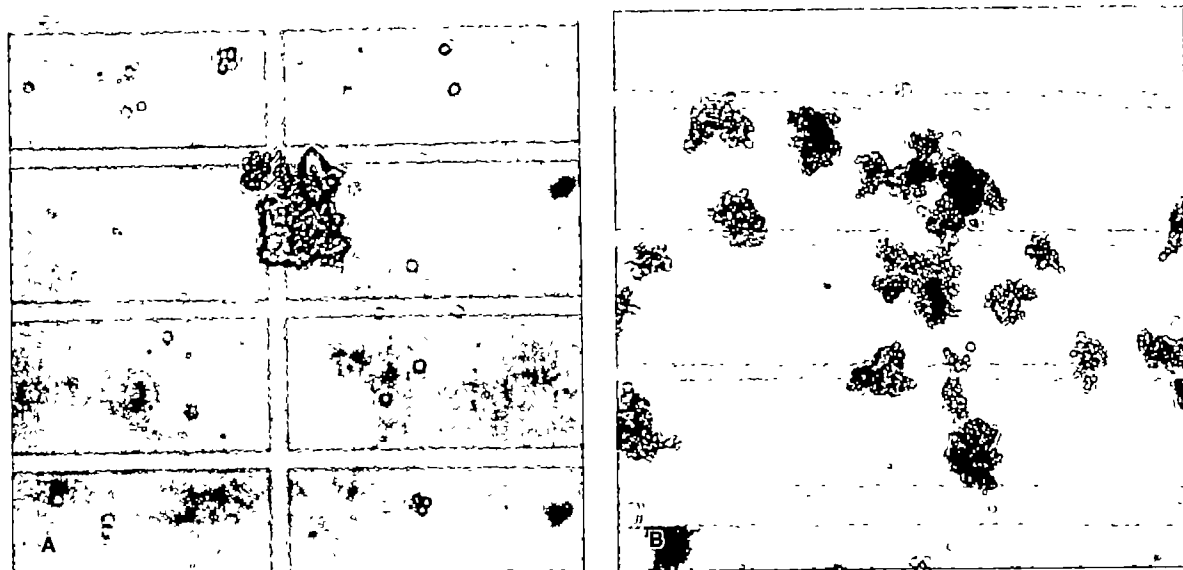


Fig. 2 Development of COM aggregates in a synthetic urine containing citrate and 0.2 g/l mucin. ($\times 400$). (A) COM crystals on mucin particle. (B) Agglomerates developed on mucin particles

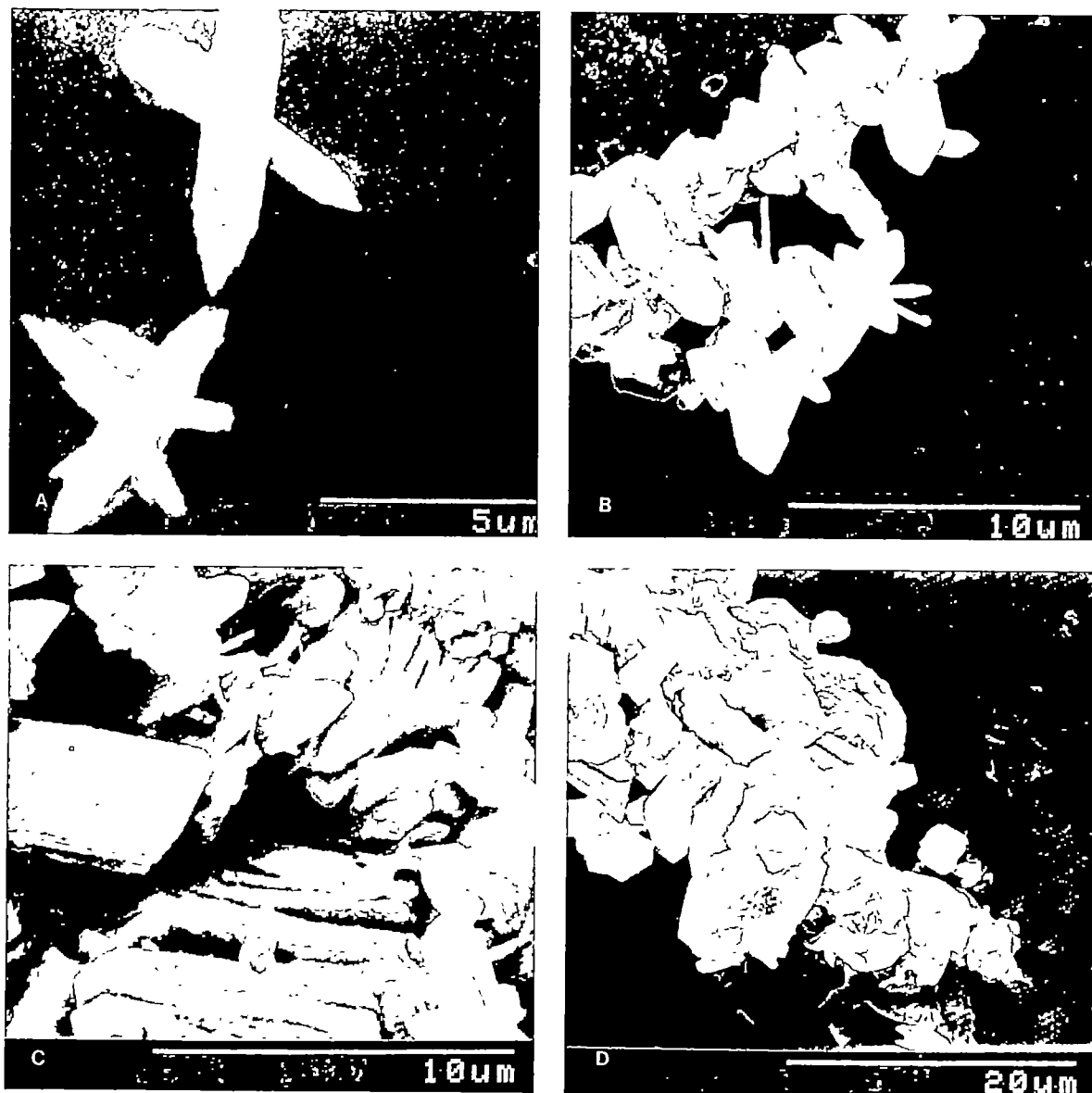


Fig. 3 Development of COM aggregates in a synthetic urine without (A–C) and with citrate (D) present. (A) Individual crystals formed at the commencement of the process (B) Loose agglomerates. (C) Detail of a compact agglomerate (D) Compact agglomerates formed from a citrate-containing system

agglomerates formed from a mucin-containing synthetic urine.

Precipitation of solutions containing increased concentrations of CaCl_2 and $\text{Na}_2\text{C}_2\text{O}_4$ proceeded in the same way as precipitation of the standard A and B solutions, but the development of agglomerates was faster. Their crystalline structure was, however, identical in both conditions.

Discussion

Crystals formed on the semi-batch precipitation from a synthetic urine examined under these conditions were typical of calcium oxalate monohydrate (COM) crystals. Formation of calcium oxalate dihydrate (COD) was not observed. In contrast, the formation of a mixture consisting of

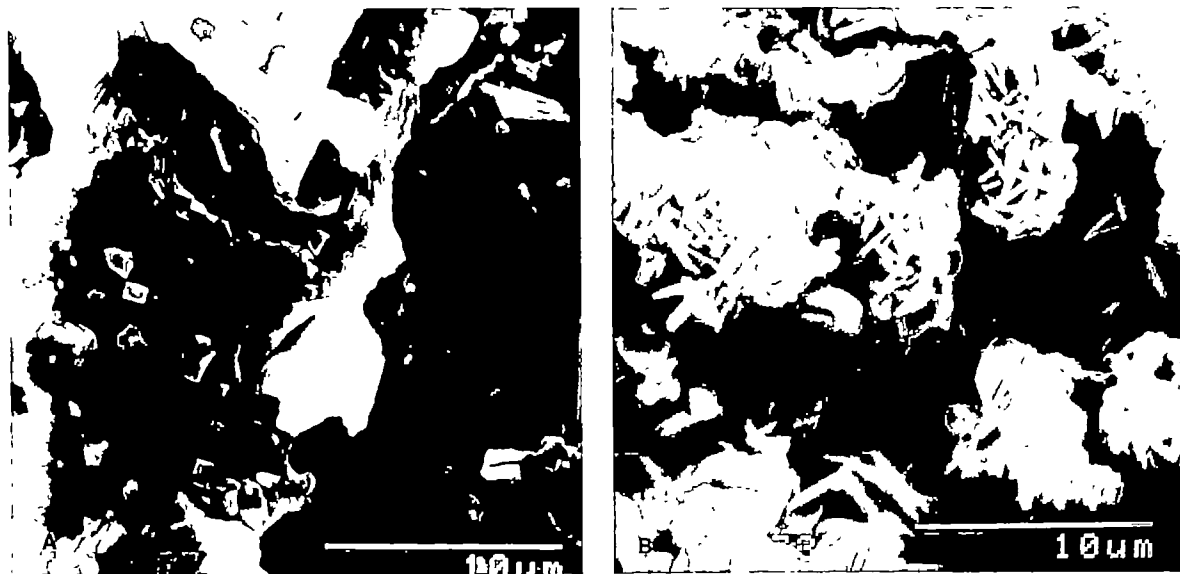


Fig. 4 Development of COM agglomerates in a synthetic urine containing citrate and 0.2 g/l mucin. (A) First crystals formed on mucin particle. (B) Spherical formations on agglomerate surface

COM, COD and COT from batch and continuously precipitated solutions of similar composition to that employed in the present work, but with a slightly higher pH, was reported by Gardner (1978), Drach *et al.* (1978), Rodgers and Garside (1981), Brečević *et al.* (1986) and Škrtić *et al.* (1987). This discrepancy may be due to slight differences in reaction conditions, but the different mode of precipitation may also play a part.

The formation and development of COM agglomerates on the semi-batch precipitation of a synthetic urine and of pure solutions as described by Millan *et al.* (1992) and Grases *et al.* (1992) were identical. Briefly, individual elongated COM crystals appearing first in the precipitating system had served as a substrate upon which new crystals were formed. This process resulted in small aggregates composed of elongated intergrown crystals that were often arranged in peculiar patterns within a particle. During further precipitation these crystals developed by lateral growth into plate-like interconnected crystals. New crystals that originated on the surface and/or tips of the parent crystals gradually became integrated into a complex agglomerate structure. After some time, particles consisting of innumerable intergrown and interconnected crystals were formed. The complex crystalline structure of these agglomerates cannot be wholly explained by a mechanism of secondary agglomeration, *i.e.*

by an incidental sticking together of crystals and their later cementation in place, although individual crystals formed separately in the solution attached to an agglomerate can also be observed. Such crystals, however, represent a small fraction of the total number of crystals forming an agglomerate. Hence, primary agglomeration represents an important, if not decisive, mechanism of COM agglomerate development and secondary agglomeration is of lesser consequence.

Citrate ions prevent the formation of large COM agglomerates by inhibiting either crystal growth or agglomeration or, more probably, both processes simultaneously (Curreri *et al.*, 1981; Nakayawa *et al.*, 1981; Ryall *et al.*, 1981; Grases *et al.*, 1988; Grases and Costa-Bauzá, 1990). Due to a qualitative evaluation of the agglomeration process employed in the present work, no firm conclusion can be drawn in that respect, but the observed suppression of new crystals forming on the parent crystals in the presence of citrate ions is consistent with the reported inhibition of agglomeration.

Mucin forms in water a colloidal solution containing small amorphous particles of this compound dispersed in the volume of liquid. Mucin particles, when present in a precipitating system, cause preferential formation of COM crystals on their surface and suppress crystal formation in the solution bulk. Hence, the surface of mucin particles

effectively promotes nucleation of COM crystals from a system supersaturated with respect to calcium oxalate.

These observations enable us to draw the following conclusions on the mechanism of COM renal stone development: (i) COM is formed on the semi-batch precipitation carried out at physiological conditions; (ii) primary agglomeration plays an important role in the development of COM agglomerates from a synthetic urine; (iii) citrate ions inhibit, but do not stop, the agglomeration process; (iv) mucoprotein particles serving as a substrate promote the formation of new COM crystals; (v) agglomeration proceeds faster in a system containing a higher concentration of calcium oxalate. Conclusions (ii), (iii) and (iv) are consistent with results reported by Lonsdale (1968), Curreri *et al.* (1981), Nakayawa *et al.* (1981), Ryall *et al.* (1981), Grases *et al.* (1988) and Grases and Costa-Bauzá (1990).

Although information on the crystalline structure of COM renal calculi is limited, at least 2 different types of stone can be distinguished: (i) calculi exhibiting a compact fracture surface where crystals are arranged in an apparently unorganised manner with no evidence of fine crystalline structure (Oren *et al.*, 1984); (ii) calculi displaying a clearly visible fine crystalline structure on the fracture surface (Kim and Johnson, 1981; Cifuentes, 1984). The crystalline structure of renal stones of the latter type closely resembles the structure of agglomerates that were formed in this study. Therefore, the second type of COM calculi, at least, could be formed by the mechanism suggested by Grases *et al.* (1992): a polycrystalline nucleus of a renal calculus develops through increasing the number of composing crystals by primary agglomeration, whereas the size of crystals increases due to ordinary crystal growth. The mucoproteins adsorbed on a part of the exposed surface of the calculus stop further growth of covered crystals as they are no longer in contact with a supersaturated fluid. However, the mucoprotein layer promotes the formation of new crystals which then start to grow and multiply by the same mechanism as described above. The conclusions inferred from these experiments support, or at least are consistent with, the suggested mechanism of the development of COM renal calculi.

The COM agglomerates formed on the semi-batch precipitation from a synthetic urine exhibit a crystalline structure similar to the type of renal stones displaying a fine crystalline structure on the fracture surface. The mechanism responsible for the development of these agglomerates is primary

agglomeration in conjunction with secondary agglomeration that, however, plays a comparatively minor role. The surface of mucoprotein particles strongly promotes nucleation of COM crystals. Experimental results support the mechanism of renal stone development based on a combination of primary agglomeration and nucleation promoted by a mucoprotein layer partially covering the exposed surface of a calculus.

Acknowledgement

Financial support from the University of the Balearic Islands (L. Masárová) and the Dirección General de Investigación Científica y Técnica, grants No. SAB 91-0040 (O. Söhmel), PB-89-0423 is gratefully acknowledged.

References

- Brečević, L., Škrčić, D. and Garside, J. (1986). Transformation of calcium oxalate hydrates. *J. Crystal Growth*, **74**, 399–408.
- Buckley, H. E. (1951) *Crystal Growth*. New York: Wiley
- Cifuentes, L. (1984). *Composición y Estructura de los Cálculos Renales*. Barcelona: Salvat Editors.
- Curreri, P. A., Onoda, G. and Finlayson, B. (1981). A comparative appraisal of adsorption of citrate on whewellite seed crystals. *J. Crystal Growth*, **53**, 209–214.
- Drach, G. W., Randolph, A. D. and Miller, J. D. (1978). Inhibition of calcium oxalate dihydrate crystallization by chemical modifier. *J. Urol.*, **119**, 99–103.
- Finlayson, B. (1978). Physicochemical aspects of urolithiasis. *Kidney Int.*, **13**, 344–360.
- Gardner, G. L. (1978). Effect of pyrophosphate and phosphonate anions on the crystal growth kinetics of calcium oxalate hydrates. *J. Phys. Chem.*, **82**, 864–870.
- Grases, F. and Costa-Bauzá, A. (1990). Study of factors affecting calcium oxalate crystalline aggregation. *Br. J. Urol.*, **66**, 240–244.
- Grases, F., Millán, A. and García-Raso, A. (1988). Polyhydroxycarboxylic acids as inhibitors of calcium oxalate crystal growth. relation between inhibitory capacity and chemical structure. *J. Crystal Growth*, **89**, 496–500.
- Grases, F., Millán, A. and Söhmel, O. (1992) Role of agglomeration in calcium oxalate monohydrate uroliths development *Nephron*. (In press).
- Jones, A. G. (1989) Agglomeration during crystallization and precipitation from solution. In *Fifth International Symposium on Agglomeration*. Institute of Chemical Engineers Symposium Series. Pp. 131–143. Rugby: Institute of Chemical Engineers.
- Kim, K. M. and Johnson, F. B. (1981). Calcium oxalate crystal growth in human urinary stones. *Scanning Electron Microscopy*, **III**, 147–154.
- Lonsdale, K. (1968). Epitaxy as a growth factor in urinary calculi and gallstones. *Nature*, **217**, 56–58.
- Millán, A., Grases, F. and Söhmel, O. (1992) Semi-batch precipitation of calcium oxalate monohydrate. *Cryst. Res. Technol.* (In press).
- Nakayawa, Y., Abram, V., Kézdy, F. J. *et al.* (1981). Purification and characterization of the principal inhibitor of calcium oxalate monohydrate crystal growth in human urine. *J. Biol. Chem.*, **258**, 12594–12600.

- Oren, A., Husdan, H., Cheng, P.-T. *et al.* (1984). Calcium oxalate kidney stones in patients on continuous ambulatory peritoneal dialysis. *Kidney Int.*, **25**, 534–538.
- Robertson, W. G., Peacock, M., Marshall, R. W. *et al.* (1976). Saturation-inhibition index as a measure of the risk of calcium oxalate stone formation in the urinary tract. *N. Engl. J. Med.*, **294**, 249–252.
- Robertson, W. G., Scurr, D. S. and Bridge, M. (1981). Factors influencing the crystallization of calcium oxalate in urine—Critique. *J. Crystal Growth*, **53**, 182–194.
- Rodgers, A. L. and Garside, J. (1981). The nucleation and growth kinetics of calcium oxalate in the presence of some synthetic urine constituents. *Invest. Urol.*, **18**, 484–488.
- Ryall, R. L., Harnett, R. M. and Marshall, V. R. (1981). The effect of urine, pyrophosphate, citrate, magnesium and glucosaminoglycans on the growth and aggregation of calcium oxalate crystals *in vitro*. *Clin. Chim. Acta*, **112**, 349–356.
- Schneider, H. J. (1985). *Pathogenesis of urolithiasis*. In *Urolithiasis, Etiology, Diagnosis*, ed. Schneider, H. J., Pp 206–207. Berlin: Springer-Verlag.
- Škrtić, D., Fíředi-Milhofer, H. and Marković, M. (1987). Precipitation of calcium oxalate from high ionic strength solutions VII. The influence of glutamic acid. *J. Crystal Growth*, **80**, 113–120.
- von Smoluchowski, M. (1918). Mathematical theory of the kinetics of coagulation of colloidal systems. *Z. Physik. Chem.*, **92**, 129–168.

The Authors

- F Grases, PhD, Professor, Department of Chemistry.
 L Masárová, PhD, Department of Inorganic and Organic Chemistry, Comenius University, Bratislava, Czechoslovakia.
 O Šňhel, DSc, Department of Inorganic Processes, VSChT, Pardubice, Czechoslovakia.
 A Costa-Bauzá, PhD, Department of Chemistry.
 Requests for reprints to: F. Grases, Department of Chemistry, Faculty of Sciences, University of Balearic Islands, 07071 Palma de Mallorca, Spain.

Urological Complications Following Live Donor Kidney Transplantation: Effect of Urinary Schistosomiasis

A. A. SHOKEIR, M. A. BAKR, T. A. EL-DIASTY, M. A. SOBH, F. E. MOUSTAFA, A. E. EL-AGROUDI and M. A. GHONEIM

Urology and Nephrology Centre, Mansoura University, Mansoura, Egypt

Summary—Urological complications were studied in 310 live donor kidney transplants. All recipients and donors were investigated for urinary schistosomiasis by examining tissue obtained intra-operatively from the donor's ureter or the patient's bladder. Schistosomiasis was histologically documented in 76 cases (patient's bladder (46), donor's ureter (9), both (21)). The incidence of urological complications was 11/76 (15%) in the schistosomal group and 14/234 (6%) in the non-schistosomal group; this was statistically significant. Among the schistosomal patients, the site of infestation had no statistically significant effect on the incidence of urological complications. No deaths or graft losses were directly attributable either to these complications or to their surgical correction.

The frequency, aetiology and management of urological complications following renal transplantation have been reported by Malek *et al.* (1973) and Mundy *et al.* (1981). Schistosomiasis affects approximately 200 million people in Africa, the Middle East, South-East Asia and South America (Weeden *et al.*, 1982). It can lead to the development of irreversible pathological changes in the urinary tract (Ghoneim, 1984). Information on the effect of urinary schistosomiasis on the frequency and nature of urological complications following renal transplantation is limited. We present our experience with urological complications that developed among 310 consecutive live donor renal transplants. Special emphasis is placed on the potential impact of urinary schistosomiasis on the incidence, type and methods of management of such complications.

Patients and Methods

Between March 1976 and March 1991, 480 renal transplantations were carried out in this Centre. Of these, the last consecutive 310 cases were studied

for evidence of urinary schistosomiasis by examination of tissue obtained intra-operatively from the donor's ureter and the recipient's bladder. Paraffin blocks were prepared and sections were stained by haematoxylin and eosin for examination by light microscopy. A diagnosis of schistosomiasis was established when *Schistosoma* eggs were seen in either specimen.

The patients were followed up for a mean period of 33 months (range 6–168). In addition to clinical examination and routine assessment of the graft function, isotope renography and ultrasonography were of particular help in the diagnosis of urological complications. The latter provided evidence of perirenal collection or obstruction of the pelvicaliceal system. It was also indispensable for diagnostic aspiration of a suspected collection to determine its chemical nature by quantitative estimation of creatinine content. Intravenous urography (IVU) was considered if renal function was not markedly impaired. More invasive procedures such as ascending cystography, retrograde ureterography, graft percutaneous nephrostomy (PCN) and antegrade study were used as necessary.

Statistical analyses were performed with an

independent *t* test, chi-squared and Fisher's exact tests.

Results

Patients were stratified into 2 groups according to the histopathological findings: schistosomal group (76 patients; 25%) and non-schistosomal group (234 patients; 75%). *Schistosoma* eggs were detected in the bladders of 46 recipients, in the ureters of 9 donors and in both in 21 cases.

All patients had received live related donor kidneys and the majority had one-haplotype HLA match. Table 1 summarises the demographic characteristics of donors and recipients of the 2 groups. Both were comparable regarding age and sex of donors and recipients, duration of pre-transplant dialysis and prior blood transfusions. The immunosuppressive regimens and the techniques employed for the re-establishment of urinary continuity were also essentially similar.

The urological complications are listed in Table 2: 25 were recorded, an incidence of 8%. Eleven complications (15%) were seen among the schistosomal group and 14 (6%) among the non-schistosomal group; this was statistically significant ($P < 0.05$). It was observed that the site of schistosomal infestation did not affect either the incidence or the type of urological complications. Furthermore, the surgical techniques used to re-establish

urinary tract continuity had no impact on the incidence of urological complications (Table 3).

The various approaches used for the correction of these complications are summarised in Table 4.

Two patients developed a urinary leak from the cystostomy incision. One was treated successfully by an indwelling urethral catheter for 1 week while the other required an open repair.

Ureteric fistulae developed in 6 patients. In all but 1 case a graft PCN was initially inserted for adequate drainage and prevention of wound sepsis. In 1 patient drainage was sufficient for prompt healing without stricture formation (Fig. 1). In the remainder, surgical intervention was necessary, the nature of which was based on the length and viability of the ureter as judged during exploration. A ureterovesical reimplantation was feasible in 2 patients, a Boari flap was necessary in 2 (Fig. 2) and a ureteroureteric anastomosis was employed in 1. In the latter case, however, the repair was complicated by urinary leakage and fistula formation and an ileal replacement of the ureter was carried out.

Intrinsic ureteric obstruction was seen in 4 patients. The obstruction was due to axial rotation of the ureter in 1 patient (Fig. 3); this was successfully corrected and reimplanted into the bladder. Three patients developed distal ureteric strictures, of whom 2 were treated by ureteroureteric anastomosis and the third by a Boari flap. These latter 3 patients developed recurrent obstruction

Table 1 Characteristics of Donors and Recipients of Schistosomal and non-Schistosomal Renal Transplants (n = 310)

Factors analysed	Schistosomal group (n = 76)		Non-schistosomal group (n = 234)	
Donor's age (years)	42 ± 5		41 ± 6	
Donor's sex (male to female ratio)	40/36		120/114	
Recipient's age (years)	29 ± 8		30 ± 7	
Recipient's sex (male to female ratio)	57/19		170/64	
Duration of pre-transplant dialysis (months)	35 ± 8		33 ± 6	
Prior transfusions (units)	3.2 ± 2		3.1 ± 2.5	
Immunosuppression	No.	%	No.	%
Azathioprine + corticosteroids	45	59	133	57
Cyclosporin + corticosteroids	23	31	72	31
Triple immunosuppression	8	10	29	12
Primary urinary tract procedures				
Leadbetter-Politano	28	37	57	24
Lich-Gregoir	44	58	160	69
Ureteroureteric	4	5	17	7

Table 2 Urological Complications

Complications	Schistosomal group (n=76) No. of patients	Non-schistosomal group (n=234) No. of patients	Total
Bladder leak	1	1	2
Ureteric fistula	4	2	6
Intrinsic ureteric obstruction	2	2	4
Stone in the graft	—	1	1
Bladder stone	1	—	1
Urethral stricture	1	1	2
Lymphocele	2	7	9
Total	*11 (15%)	*14 (6%)	25 (8%)

* ($\chi^2 = 4.5$, $P < 0.05$) Chi-squared test

and a tertiary interference was necessary using a pyeloureteric anastomosis in 1 case and an ileal ureter in 2.

Lymphocele-induced ureteric obstruction occurred in 9 patients. Three were treated by percutaneous drainage, with excellent results in 2. The remainder required marsupialisation into the peritoneal cavity.

The development of these complications and the surgical procedures required for their correction were not associated with or followed by either mortality or graft loss.

Discussion

A review of the literature indicates that the incidence of urological complications after renal

transplantation ranges between 29.8% (Maclean *et al.*, 1969) and 2.4% (Salvatierra *et al.*, 1977). This wide difference may be attributed to the methods of reporting. However, more recent studies demonstrate a decline in their frequency, with a reported incidence of less than 10% (Shah *et al.*, 1988; Thrasher *et al.*, 1990). The mortality directly attributed to urological complications has been reviewed by Malek *et al.* (1973) and was shown to range from 0 to 100%. In a series of 1000 renal transplants, Mundy *et al.* (1981) reported a mortality rate of 22% following surgical correction of obstructive uropathies and urinary fistulae that had developed after renal transplantation. They also stated that patients who received a living related allograft had a lower mortality rate but a similar incidence of ureteric obstruction when compared

Table 3 Urological Complications in Relation to Surgical Techniques

Complications	Leadbetter-Politano (n=85)		Lich-Gregoir (n=204)		Uretero-ureteric (n=21)	
	Schist. (n=28)	Non-schist. (n=57)	Schist. (n=44)	Non-schist. (n=160)	Schist. (n=4)	Non-schist. (n=17)
Bladder leak	1	1	—	—	—	—
Ureteric fistula	2	—	1	1	1	1
Intrinsic ureteric obstruction	1	1	1	1	—	—
Stone in the graft	—	1	—	—	—	—
Bladder stone	1	—	—	—	—	—
Urethral stricture	—	—	—	2	—	—
Lymphocele	1	1	1	5	1	—
Total	6	4	3	9	2	1
Significance	* $\chi^2 = 3.756$ $P = 0.052$		* $\chi^2 = 0.0887$ $P = 0.765$		** $P = 0.079$	

* Chi-squared test.

** Fisher's exact test.

Table 4 Treatment of Urological Complications

Complications	Treatment	Result
Bladder leak (2)	Urethral catheter (1)	Excellent
	Primary repair of bladder (1)	Excellent
Ureteric fistula (6)	Graft PCN (1)	Excellent
	Uretero-vesical reimplantation (2)	Excellent in both
	Boari flap (2)	Excellent in both
	Ureteroureteric anastomosis (1)	Developed recurrent fistula that was treated by an ileal ureter
Intrinsic ureteric obstruction (4)	Ureterovesical reimplantation (1)	Excellent
	Ureteroureteric anastomosis (2)	One patient developed recurrent obstruction and was treated by pyeloureteric anastomosis; the other patient developed extensive obstruction of the whole ureter and was treated by an ileal ureter.
	Boari flap (1)	Developed recurrent obstruction and was treated by a second Boari flap which led to obstruction and was treated by an ileal ureter.
Lymphocele (9)	Percutaneous drainage (3)	Excellent in 2 cases and recurrence of lymphocele in 1 case that was treated by marsupialisation
	Marsupialisation (6)	Excellent
Stone in the graft (1)	Conservative (1)	Static
Bladder stone (1)	Crushing (1)	Recurrence of a big bladder stone that was treated by open cystolithotomy
Urethral stricture (2)	VIU (2)	Excellent

with recipients of cadaveric kidneys. In the present series the rate of urological complications was 8%, a figure which compares favourably with the current standards. Despite the fact that some of our patients required complex and repeated surgical intervention, no deaths or graft losses were related to the

urological complications or resulted from their surgical correction.

It is interesting to note that an ileal ureter was successfully used for the correction of 3 recurrent urological complications after renal transplantation. Mundy *et al.* (1981) reported 4 such cases, but

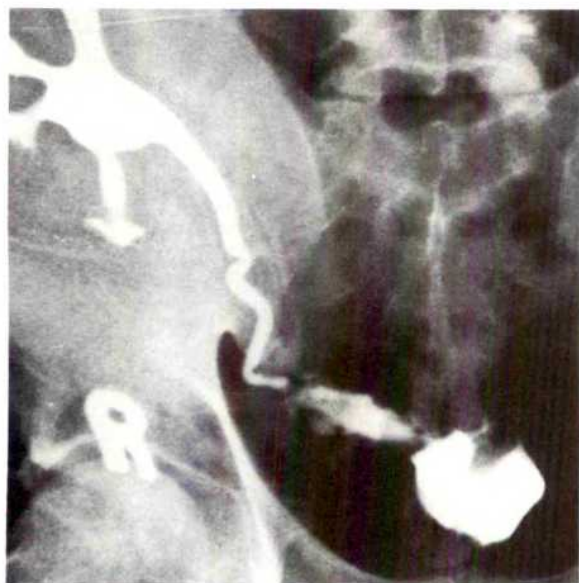


Fig. 1 Antegrade pyelography showing small ureteric leak 2 weeks after transplantation.



Fig. 2 Early post-operative antegrade pyelography after Boari flap procedure for treatment of ureteric fistula.

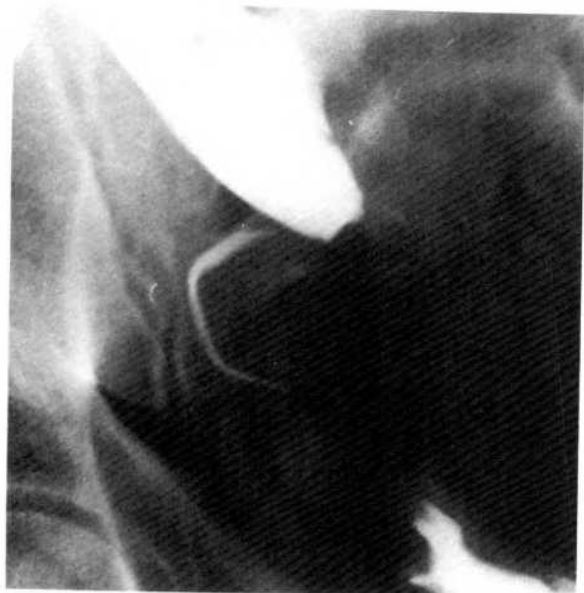


Fig. 3 Antegrade pyelography showing marked hydronephrosis due to axial rotation of ureter.

2 of these patients died from peritonitis as a result of disruption of the enteroanastomosis. Goodwin (1987) also suggested that an ileal ureter could be used in selected cases for the management of recurrent complications following renal transplantation, although he did not report a specific experience.

Schistosomal subjects are not usually considered as potential kidney donors unless extensive investigations confirm the absence of gross structural abnormalities in their urinary tract. Similarly, schistosomal recipients are evaluated for the distribution and severity of urinary fibrotic lesions to ensure their long-term eligibility for a renal graft. There are few reports on the effect of urinary schistosomiasis on the incidence of urological complications after renal transplantation. Weeden *et al.* (1982) reported 6 patients who were infested with *Schistosoma haematobium* and who underwent live donor kidney transplantation. Three developed complications which appeared to be related to their schistosomal infestation. Hefty and McCorkell (1986) diagnosed schistosomiasis in 4 recipients and in 12 kidney donors in 67 consecutive kidney transplantations. They reported no surgical complications related to schistosomiasis in this group.

In the present study, since the diagnosis of schistosomiasis was based upon the demonstration of *Schistosoma* eggs in the recipient's bladder or the

donor's ureter, the actual incidence of the disease may have been underestimated. The estimated frequency of 15% among this subpopulation of recipients is still acceptable and does not contraindicate renal transplantation since it did not affect either the patient or the graft survival. The current range of surgical methods, the feasibility of percutaneous techniques and the availability of a wide range of antimicrobial therapies make it possible for complex and repeated surgical interventions to be carried out without inflicting further risks on either the patient or the transplanted kidney.

References

- Ghoneim, M. A. (1984). Bilharziasis: the lower genitourinary tract. In *Tropical Urology and Renal Disease*, ed. Husain, I. Chapter 16, pp. 261–280. Edinburgh: Churchill Livingstone.
- Goodwin, W. E. (1987). Experiences with intestine as a substitute for the urinary tract. In *Bladder Reconstruction and Continent Urinary Diversion*, ed. King, L. R., Stone, A. R. and Webster, G. D. Chapter 2, pp. 9–29. Chicago: Year Book Medical Publishers.
- Hefty, T. R. and McCorkell, S. J. (1986). Schistosomiasis and renal transplantation. *J. Urol.*, **135**, 1163–1166.
- MacLean, L. D., Mackinnon, K. G., Inglis, F. G. *et al.* (1969). When should renal allografts be removed? *Arch. Surg.*, **99**, 269–274.
- Malek, G. H., Uehling, D. T., Daouk, A. A. *et al.* (1973). Urological complications of renal transplantation. *J. Urol.*, **109**, 173–176.
- Mundy, A. R., Podesta, M. L., Bewick, M. *et al.* (1981). The urological complications of 1000 renal transplants. *Br. J. Urol.*, **53**, 397–402.
- Salvatierra, O., Olcott, C., Amend, W. J., Jr. *et al.* (1977). Urologic complications of renal transplantation can be prevented or controlled. *J. Urol.*, **117**, 421–424.
- Shah, S., Nath, V., Gopalkrishnan, G. *et al.* (1988). Evaluation of extravesical and Leadbetter-Politano ureteroneocystostomy in renal transplantation. *Br. J. Urol.*, **62**, 412–413.
- Thrasher, J. B., Temple, D. R. and Spees, E. K. (1990). Extravesical versus Leadbetter-Politano ureteroneocystostomy: a comparison of urological complications in 320 renal transplants. *J. Urol.*, **144**, 1105–1109.
- Weeden, D., Hopwell, J. P., Morehead, J. F. *et al.* (1982). Schistosomiasis in renal transplantation. *Br. J. Urol.*, **54**, 478–479.

The Authors

- A. A. Shokeir, MD, Lecturer in Urology.
- M. A. Bakr, MD, Consultant Nephrologist.
- T. A. El-Diasty, MD, Consultant Radiologist.
- M. A. Sobh, MD, Assistant Professor of Medicine.
- F. E. Moustafa, MD, Lecturer in Pathology.
- A. E. El-Agroudi, Resident in Nephrology.
- M. A. Ghoneim, MD(Hon), Professor of Urology.

Requests for reprints to: M. A. Ghoneim, Urology and Nephrology Centre, Mansoura, Egypt.

Management of Impacted Upper Ureteric Calculi: Results of Lithotripsy and Percutaneous Litholapaxy

A. SRIVASTAVA, R. AHLAWAT, A. KUMAR, R. KAPOOR and M. BHANDARI

Department of Urology, Sanjay Gandhi Post-Graduate Institute of Medical Sciences, Lucknow, India

Summary—Despite the availability of lithotripsy and endourology, clear guidelines on the management of impacted upper ureteric calculi are lacking. In this study, 51 upper ureteric calculi treated with *in situ* extracorporeal shock wave lithotripsy (ESWL) were classified according to the degree of impaction as indicated by proximal back pressure changes. Patients with mild proximal hydronephrosis (or none at all) had a success rate of 93% but only 35% of those in the impacted group (moderate to severe hydronephrosis) had a successful outcome. A percutaneous antegrade approach to 29 impacted upper ureteric calculi resulted in total clearance in 23 cases; 4 other patients were rendered stone-free following additional procedures, an overall success rate of 93%. The only complication was a ureteric stricture in 1 patient. We recommend the percutaneous approach in the management of impacted upper ureteric calculi.

Impacted upper ureteric calculi present the urologist with a challenge. ESWL following transvesical endoscopic manipulation is impracticable for impacted and hard stones (Dretler and Weinstein, 1988). The success rate of retrograde ureteroscopy for upper ureteric calculi is low, and percutaneous litholapaxy (PCNL) seems a better solution despite its invasive nature.

Patients and Methods

Between October 1988 and October 1990, 51 solitary upper ureteric calculi were treated by *in situ* ESWL without prior endoscopic intervention. During the same period, percutaneous litholapaxy was carried out in 29 patients with upper ureteric calculi. The pre-treatment intravenous urograms were studied to assess the degree of hydronephrosis, which was taken as an indicator of the degree of impaction of the calculus. Normal or blunted calices were recorded as normal or mild hydronephrosis (group A) and caliceal clubbing or ballooning was regarded as moderate to severe hydronephrosis (group B). Of

47 urograms in patients treated with *in situ* ESWL, 27 were allocated to group A and 20 to group B; all 29 renal units undergoing percutaneous extraction showed moderate to severe hydronephrosis.

In situ ESWL was performed with the Lithostar, a second-generation lithotripter. All patients were treated without anaesthesia on an out-patient basis and received a maximum of 3500 shock waves in a single sitting at 17.8 to 19 kV. If necessary, the treatment was repeated 4 days later. Patients received diclofenac and an antibiotic during and after treatment. Failure to fragment the stone in 2 sittings was regarded as a treatment failure. Patients were followed up 2 weeks after the procedure and then 4 and 6 weeks later, with plain abdominal X-ray. Fragments > 5 mm were treated similarly during follow-up visits.

The percutaneous procedure was preceded by endoscopy in an attempt to manipulate the stone. An end-hole ureteric catheter was passed up to the stone and disimpaction attempted both mechanically and with saline injected through the catheter. If this failed, an attempt was made to bypass the stone with a guide wire passed up the ureteric catheter. If this too was unsuccessful, the ureteric catheter was left below the stone. Percutaneous

puncture was carried out under fluoroscopic control after opacification of the system with a chiba needle puncture in cases where the anatomy was not well delineated by contrast administered through the ureteric catheter. The site of entry into the pelvicaliceal system was the lower or upper posterior middle calix, depending upon the site of the calculus and the configuration of the pelviureteric junction. The tract was dilated with Teflon or metal dilators and a 32F Amplatz sheath was used. Distilled water was used for irrigation (or 1/6 saline during electrohydraulic lithotripsy (EHL). Stones were visualised by means of a 22 or 24 F oval sheath or a 14 F ureteroscope (Storz). Stones were disintegrated by means of ultrasound or EHL before extraction. The ureteric catheter was identified in the distal ureter and pulled up into the kidney. If the distal lumen and catheter could not be identified, a guide wire was pushed through the end-hole ureteric catheter to be retrieved proximally and the ureteric catheter advanced over it. In patients with gross mucosal laceration at the impacted stone site, the catheter was exchanged with antegrade placement of a double pigtail stent. A plain abdominal X-ray and nephrostogram were performed after 48 to 72 h, prior to removing the nephrostomy tube and ureteric catheter. Patients were discharged with an indwelling stent and this was removed 4 weeks later.

Intravenous urography was performed 3 months post-operatively to assess clearance and functional status. Data were available in 49 of 51 patients undergoing *in situ* ESWL and in all 29 patients after percutaneous litholapaxy. Total clearance was classified as (A) and the presence of non-obstructing fragments <3 mm as (B). Both results were regarded as satisfactory. The persistence of significant residue was categorised as a treatment failure. Statistical analysis was done using analysis of variance and chi-squared statistics with continuity correction factor.

Results

Ureteric calculi treated with ESWL in patients with none or mild hydronephrosis measured an average of 82 mm² and were smaller than the average stone mass in patients with moderate to severe hydronephrosis (average 111 mm²). The former group required an average of 3311 shock waves over 1.2 sittings and the latter received an average of 8852 shock waves over 2.6 sittings (Table 1). The higher number of shock waves required by the latter group reflected the difficulty

Table 1 Details of Treatment.

Category	Average size (mm ²)		Average no. of sittings	Shock waves $\pm$ SEM
Degree of impaction*				
Not impacted	27	82	1.2	3311 $\pm$ 426
Impacted	24	111	2.6	8852 $\pm$ 1487†
Size (mm ²)				
< 100	38	67	1.6	4866 $\pm$ 538
101–400	13	168	2.2	8461 $\pm$ 2347‡

*As on pre-treatment urogram.

† $P < 1\%$ (analysis of variance).

‡ $P < 5\%$ (analysis of variance).

of disintegration ($F = 16.402$; $P < 1\%$). In 25 of 27 unimpacted stones (93%) the outcome was successful but only 7 of 20 stones (35%) in patients with moderate to severe hydronephrosis were treated successfully by ESWL (Table 2; $\chi^2 = 14.988$; $P < 1\%$). In these cases the upper part of the calculus in contact with the water head in the dilated proximal ureter fragmented earlier, while the distal part or core was fragmented with difficulty or not at all (Fig. 1). Early fragmentation of the upper part resulted in the fragments floating back to the pelvicaliceal system and being retained as residue in a higher number of patients in the impacted calculi group (Table 2, Figs 2 and 3).

Of 51 ureteric calculi treated *in situ*, 38 were up to 100 mm² and 13 measured 101 to 400 mm². Larger calculi required more shock waves to achieve disintegration (8461 vs 4866; $F = 2.701$, $P < 5\%$). Satisfactory results after 3 months were achieved in 26/36 evaluable patients with smaller stones

Table 2 ESWL Treatments: Results in Sub-groups

Category	No. evaluable at 3 months	Results					
		A	B	A+B (%)	C	D	C+D (%)
Degree of impaction*							
Not impacted	27	24	1	(93)	1	1	(7)
Impacted	20	5	2	(35)	2	11	(65)
Size (mm ²)							
< 100	36	23	3	(72)	3	7	(28)
> 101	13	8	0	(62)	0	5	(39)

*As on pre-treatment urogram

A = Total clearance

B = Insignificant non-obstructive renal residue.

C = Significant renal/obstructing ureteric residue.

D = Fragmentation failure.

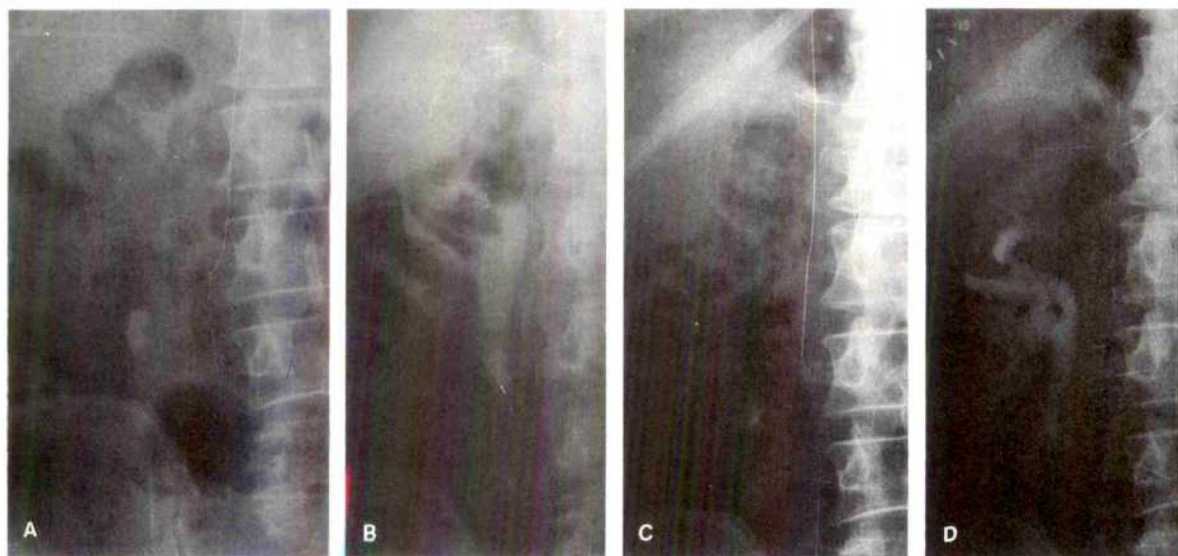


Fig. 1 Impacted upper ureteric calculus with moderate hydronephrosis (A and B) treated with 3 ESWL procedures. Patient passed stone fragments and became asymptomatic. Follow-up IVU at 3 months (C and D) revealed unfragmented core of the calculus, although hydronephrosis had disappeared.

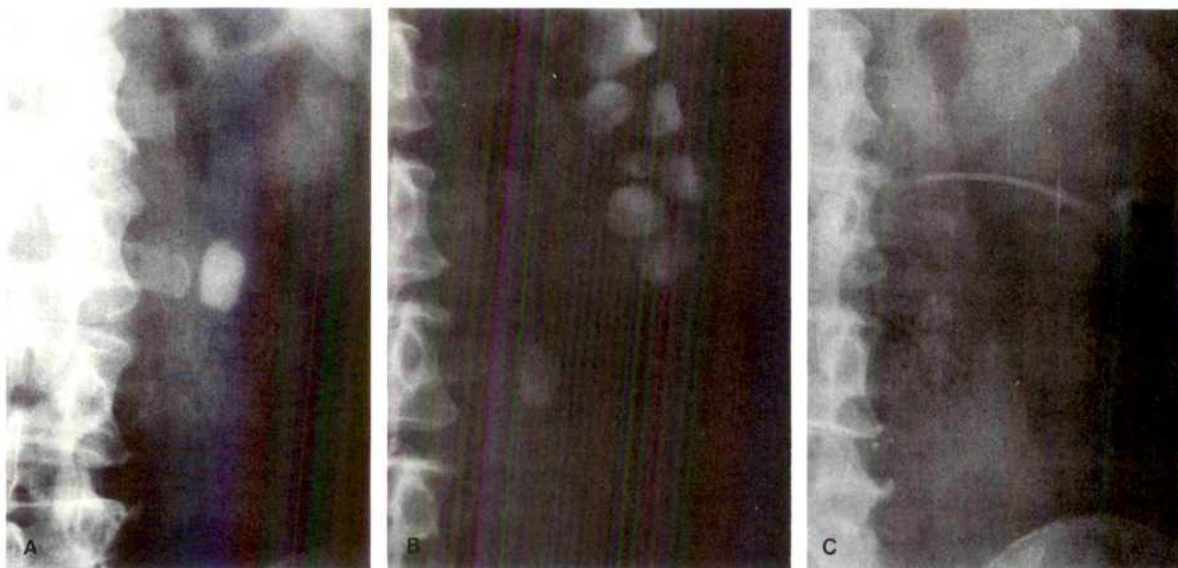


Fig. 2 Impacted upper ureteric calculus with moderate proximal hydronephrosis (A and B). Plain X-ray immediately after fragmentation (C) with gravel having migrated proximally to dilated calices (arrow).

(72%) and in 8 of 13 with larger stones (62%) ($\chi^2 = 0.133$; not significant). Thus bulk alone was not a significant variable in determining the outcome, although bigger calculi required more shock waves.

The average size of stones treated with PCNL was 196 mm² and all were associated with moderate to severe hydronephrosis. Five of these renal units

were not visualised on initial IVU and a staged procedure was carried out 3 weeks after percutaneous decompression. During endoscopic manipulation the impacted stone was pushed back in one case and bypassed in 5. A ureteric catheter was left below the calculus in the other patients. The puncture for the tract was infracostal in 18 and

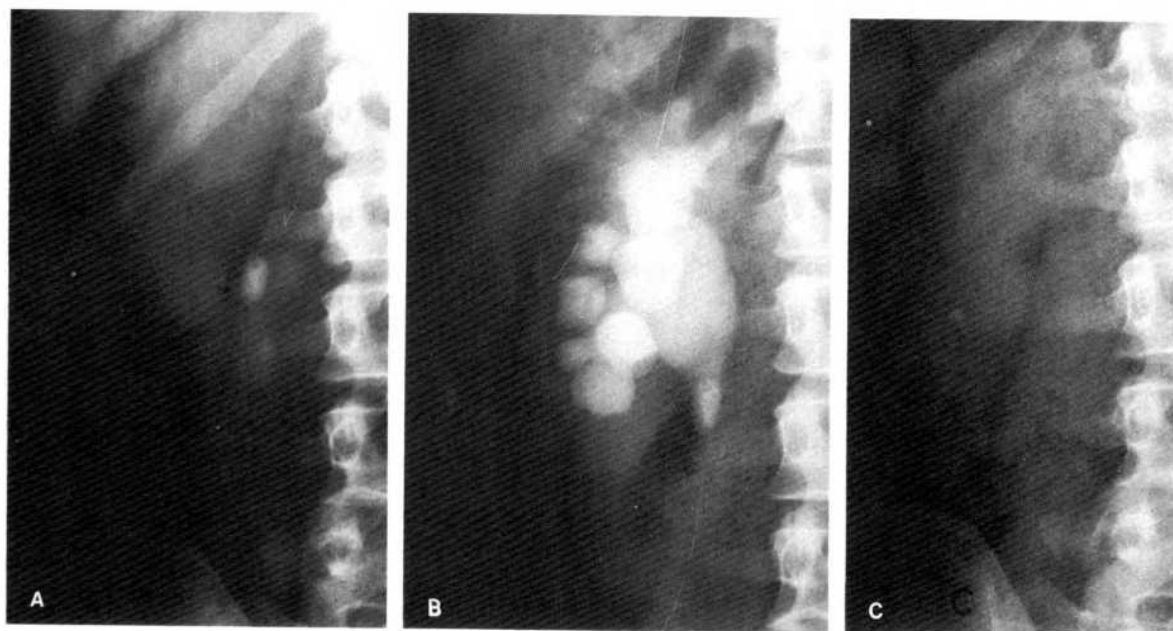


Fig. 3 Impacted calculus just below pelviureteric junction (A and B) treated with lithotripsy. Plain X-ray at 3 months reveals a fragment in inferior calyx.

between the eleventh and twelfth ribs in 11 cases. On 21 occasions the dilated upper ureter was traversed and the stone could be visualised with a 22 or 24 F oval nephroscope. A 14 F ureteroscope was used to reach the stone in 6 cases where the proximal ureter was considered too narrow for the nephroscope sheath. In 2 cases the stone could not be reached with a rigid endoscope. Apart from one case where the stone had been pushed back to the pelvis, none of the stones could be removed without disintegration from their site of impaction in the ureter. In all but 3 cases (where EHL was used electively) the calculus was disintegrated with ultrasound; 23 of these calculi were cleared with PCNL alone; 3 patients required ESWL for residual fragments and 1 underwent ureterorenoscopy for a fragment in the lower ureter. All patients requiring additional ESWL were among the first 9 cases to be so treated. Total clearance was achieved in 27/29 calculi (93%). When compared with the 35% success rate achieved with ESWL in a similar population, this was a significant improvement ($\chi^2=16.177$; $P<0.01\%$). The success rate of 79.3% with PCNL alone was significant when compared with the success rate following *in situ* ESWL ($\chi^2=8.012$; $P<1\%$). Post-operative nephrostography 48 to 72 h after the procedure occasionally showed good drainage but there was a sudden narrowing of the lumen at the site of the stone due to persisting

oedema. The insignificant nature of such narrowing was proved by a prior Whitaker test through the nephrostomy before pulling out the tube (Fig. 4). The stone could not be reached with a rigid instrument in 2 cases; this was due to a fixed kidney in one case and a low puncture site in the other. The first patient underwent ureterolithotomy and the second underwent ESWL successfully with nephrostomy *in situ*. Ureteric perforation during disintegration and retrieval of fragments occurred in 4 cases. Successful antegrade stent placement was achieved in all 4 cases by placing it over the guide wire, which was inserted from the urethral end through the end-hole ureteric catheter, retrieved under vision from the ureteric site and taken out through the nephrostomy tract. The perforations healed without complications in 3 patients but one developed a stricture and underwent ureteroureterostomy. No pulmonary complications were encountered. The average post-operative hospital stay was 6.2 days and there was no mortality.

Discussion

Impacted ureteric calculi are not likely to have a successful outcome with ESWL, though the definition of an impacted calculus is debatable (Anselmo *et al.*, 1990). Impaction has been defined as the

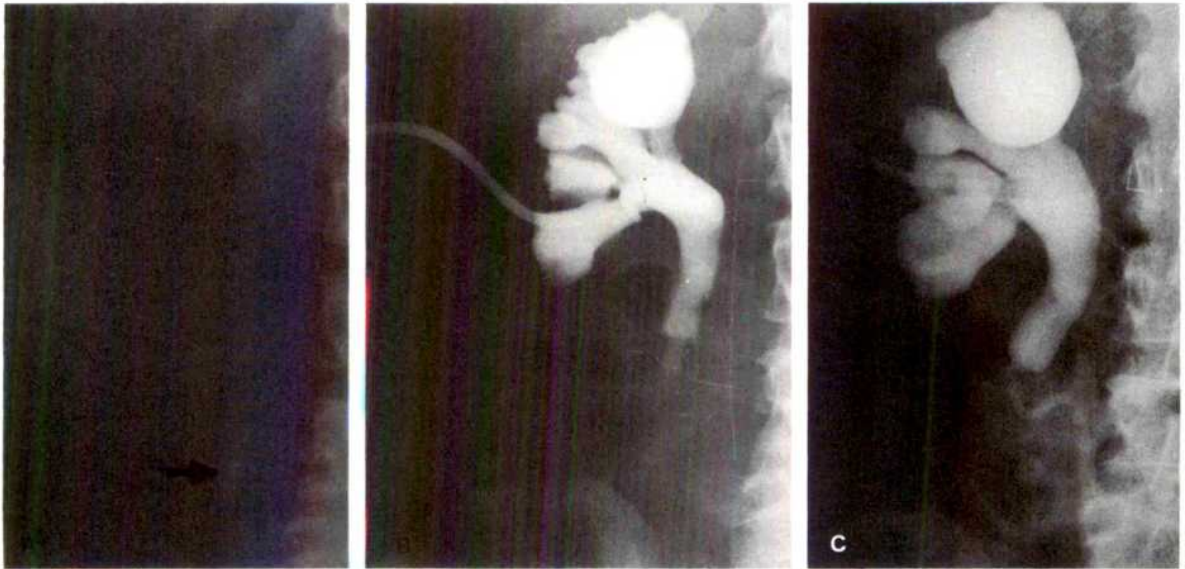


Fig. 4 Impacted upper ureteric calculus (arrow) in a patient with obstructive uropathy (A) managed initially with percutaneous nephrostomy. Antegrade study (B) shows almost complete block at the site of the stone. Antegrade study 3 days after percutaneous litholapaxy (C) shows anatomical narrowing at the same site but good drainage. Non-obstructive nature of the narrowing was proved with a Whitaker test.

inability to pass a guide wire or catheter beyond the stone (Morgentaler *et al.*, 1990).

The duration and degree of impaction can be expected to parallel the proximal back pressure changes, and patients with moderate or severe hydronephrosis are unlikely to have good results with ESWL. Patients with normal or slightly full pelvicaliceal systems had a success rate with *in situ* ESWL of 93%, which is comparable to figures for pre-ESWL endoscopic bypass or push back (Lingeman *et al.*, 1987; Liong *et al.*, 1989). Patients with

moderate to severe proximal hydronephrosis are destined to fare poorly with *in situ* ESWL, but its efficacy may be increased if the stone can be bypassed or pushed back prior to the lithotripsy (Liong *et al.*, 1989). Manoeuvres to achieve disimpaction include saline irrigation, injection of xylocaine jelly, disimpaction with ureteric catheters or a ureteroscope (Dretler and Weinstein, 1988; Evans *et al.*, 1988). Despite trying saline irrigation and guide wire manipulations through end-hole ureteric catheters before percutaneous procedures, we succeeded in disimpacting only 6/29 such calculi (21%), though a higher success rate has been reported by using semi-rigid ureteroscopes (7.2 F) together with the use of lasers (Morgentaler *et al.*, 1990).

Percutaneous litholapaxy of ureteric calculi is, in our experience, a good alternative. The proximal dilated ureter makes most such stones approachable with a 22 or 24 F nephroscope sheath (Karl-Storz), failing which a large calibre ureteroscope (14 F) may be employed.

Despite modern methods, impacted ureteric calculi and calculi lying just below the pelviureteric junction remain a problem (Dretler and Weinstein, 1988). While upper ureteric calculi without or with minimal hydronephrosis can be treated with *in situ* ESWL, impacted upper ureteric calculi have to be treated aggressively. A trial of retrograde manipulation under anaesthesia is the first step, but the

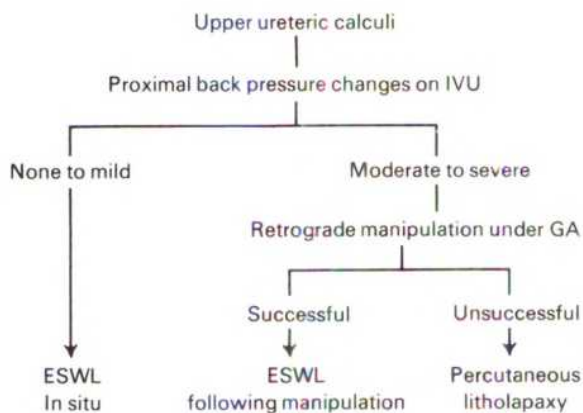


Fig. 5 Present approach to treatment of upper ureteric calculi.

procedure most likely to succeed is percutaneous litholapaxy.

Acknowledgement

We thank Mr D. Srivastava for secretarial assistance.

References

- Anselmo, G., Bassi, E., Fardella A. *et al.* (1990) Antegrade ureterolitholapaxy in the treatment of obstructing or incarcerated proximal ureteric stones. *Br. J. Urol.*, **65**, 137-140.
- Dretler, S. P. and Weinstein, A. (1988). A modified algorithm for the management of ureteral calculi: 100 consecutive cases *J. Urol.*, **140**, 732.
- Evans, R. J., Wingfield, D. D., Morollo, B. A. *et al.* (1988) Ureteral stone manipulation before extracorporeal shock wave lithotripsy. *J. Urol.*, **139**, 33.
- Lingeman, J. E., Shirrell, W. L., Newman, D. M. *et al.* (1987). Management of upper ureteral calculi with extracorporeal shock wave lithotripsy *J. Urol.*, **138**, 720.

Liong, M. L., Clayman, R. V., Gittes, R. F. *et al.* (1989) Treatment options for proximal ureteral urolithiasis; review and recommendations. *J. Urol.*, **141**, 504.

Morganstaler, A., Bridge, S. S. and Dretler, S. P. (1990). Management of the impacted ureteral calculus. *J. Urol.*, **143**, 263-266.

The Authors

A. Srivastava, MS, MCh(Urol), Senior Resident.
R. Ahlawat, MS, MCh(Urol), Associate Professor
A. Kumar, MS, MCh(Urol), Associate Professor
R. Kapoor, MS, MCh(Urol), Assistant Professor
M. Bhandari, MS(Surg), MCh(Urol), MNAMS, Professor and Head.

Requests for reprints to: M. Bhandari, Department of Urology, Sanjay Gandhi Post-Graduate Institute of Medical Sciences, Post Box 375, Raebareilly Road, Lucknow - 226 001, India.

Management of Hydatid Cysts of the Urinary Tract

S. D. SHETTY, A. AL-SAIGH, A. I. A. IBRAHIM, K. P. PATIL and C. L. BHATTACHAN

Department of Surgery, College of Medicine, King Saud University (Alha branch), and Asir Central Hospital, Abha, Saudi Arabia

Summary—Eleven patients with hydatid disease of the urinary tract have been seen in the last 5 years. Seven patients had cysts of the kidneys and 4 had large retrovesical hydatids. Seven of the 8 patients with renal hydatids presented with loin pain and mass. Three patients with renal communicating hydatids also presented with haematuria which was due to passing “grape skin” (hydatid membrane) in the urine. Two patients with retrovesical hydatids had bladder outflow obstruction and 2 had bilateral ureteric obstruction leading to uraemia. Eight of 11 patients had associated hydatids of other organs such as the liver (4 patients), peritoneal cavity (2) and lungs (1). Computed tomography was the most useful and specific investigation. In both renal and pelvic (retrovesical) hydatid cysts, endocystectomy with either partial excision or plication of the ectocyst is the standard treatment. In renal communicating hydatids the options are either nephrectomy (partial or total) or endocystectomy with closure of the communication. The use of cryocone and scolicalid agents is mandatory during surgery.

Hydatid disease is a parasitic infestation caused by the cestode *Echinococcus granulosus* and involves mainly the liver and the lungs, although no organ is immune. The disease is endemic in the Middle East (Halim and Vaezzadeh, 1980; Al-Ani and Al-Waili, 1986), some parts of Africa (Bencheikroun *et al.*, 1986) and Mediterranean countries (Gilsanz *et al.*, 1980). Kidney involvement is rare in hydatid disease and constitutes only 2 to 4% of all cases. In the last 5 years 110 cases of hydatids were seen in Asir Central Hospital, of which 7 had involvement of the urinary tract (6.4%). The evaluation of different diagnostic methods in this disease has been reported previously (Shetty *et al.*, 1992). In the present communication we highlight the clinical features and the various forms of surgical treatment that are available.

Patients and Methods

The study group comprised 11 patients and their age, sex, nationality and clinical features were reviewed. All were Saudi nationals living in rural

communities and involved in animal husbandry. There were 7 males and 4 females with a mean age of 46.5 years. Investigations included eosinophil count, indirect haemagglutination test (IHA), ultrasonography (US), intravenous urography (IVU), computed tomography (CT) and retrograde pyelography. Renal hydatids were divided into either communicating or non-communicating with the pelvic/ceal system. Hydatid cysts due to *E. granulosus* were described as unilocular as compared with multilocular cysts caused by *E. multilocularis*. These were further divided into univesicular and multivesicular cysts according to the presence or absence of daughter cysts. The surgical procedures were analysed.

Results

Clinical features (Table 1)

Abdominal pain and mass formed the commonest presenting symptom and this was present in 91% of the patients; 7 of 8 patients with renal hydatids had these symptoms localised to the loin. Three patients with renal communicating hydatids had haematuria as well, which was due to the passage of ruptured

Table 1 Clinical Features

Clinical features	No.
Abdominal pain	10
Abdominal mass	10
Haematuria	3
"Grape skin" in urine	3
Renal failure	2
Bladder outflow symptoms	2

daughter cysts ("grape skin") in the urine. Two patients with retrovesical hydatids had bladder outflow obstruction and 2 had bilateral ureteric obstruction leading to uraemia.

Involvement of other organs (Table 2)

Only 3 patients had isolated renal cysts. The remaining 8 had multi-organ involvement, of which the liver was the commonest (4) followed by the peritoneal cavity (2) and lungs (1). The right kidney was involved in 6 patients and in 1 case both kidneys were affected. All cysts except one were in the upper pole of the kidney.

The diagnostic methods used in these patients have been described by Shetty *et al.* (1992). Briefly, eosinophilia ($>4\%$) was seen in 4 patients and IHA was positive ($>1:128$) in 7 patients. Ultrasonography was diagnostic in 7 of 11 patients and mixed echogenicity was the diagnostic feature. IVU had shown a mass in 8 patients. Only 2 could be diagnosed as hydatids owing to the presence of curvilinear calcification. CT was diagnostic in 8 of 9 patients. The presence of multivesicular cysts with mixed density due to daughter cysts is characteristic of hydatid disease (Fig. 1). Retrograde pyelography confirmed the presence of communication with the collecting system in 2 patients.

Surgical procedures (Table 3)

Six of 7 renal hydatids were operated upon. Three

Table 2 Other Organs Involved in Urinary Tract Hydatid Disease

Organs	No.
Kidney only	3
Kidney + liver	2
Kidney + liver + peritoneum	1
Kidney + lungs	1
Retrovesical + liver	2
Retrovesical + liver + para-renal	1
Retrovesical + peritoneum	1
Total	11

**Fig. 1** CT scan of patient with retrovesical hydatid cyst occupying the entire pelvis and compressing the bladder.

non-communicating hydatids were treated by endocystectomy (removal of laminated membrane) with partial ectocystectomy; there were no complications (Fig. 2). Two large communicating cysts were treated by nephrectomy. In 1 patient the removal of endocysts with closure of the ectocyst resulted in a perinephric leak which required operative drainage. Three of 4 pelvic cysts were operated upon; all underwent removal of the endocyst with partial excision and plication of the ectocyst. In one of these patients, who had a pre-operative percutaneous left nephrostomy, a renocolo-cutaneous fistula developed during the post-operative period but the fistula closed spontaneously.

Discussion

Hydatid disease is endemic in Saudi Arabia, especially in the southwestern region (Hossain *et al.*, 1985; Noah *et al.*, 1986). The incidence of urinary tract hydatid disease in this region was 6.4%, which is higher than that reported elsewhere (Halim and Vaezzadeh, 1980; Karabekios *et al.*, 1989). Both sexes seem to be at risk. Our patients were a decade older than those reported by Halim and Vaezzadeh (1980) but similar in age to those reported by Al-Ani and Al-Waili (1986). The range of clinical features was similar to that reported previously (Halim and Vaezzadeh, 1980; Al-Ani and Al-Waili, 1986). Haematuria with hydatid

Table 3 Surgical Procedures

<i>Procedures</i>	<i>Type of cyst</i>	<i>No.</i>	<i>Complication</i>
Endocystectomy, partial ectocystectomy	RNC	3	Nil
Endocystectomy, closure of ectocyst	RC	1	Perinephric leak
Nephrectomy	RC	2	Nil
Endocystectomy, partial excision/plication of ectocyst	RV	3	Reno-colo-cutaneous fistula from (L) PCN in 1 patient
Total		9*	

* 2 patients did not have surgery.

RNC = Renal non-communicating.

RC = Renal communicating.

RV = Retrovesical.

PCN = Percutaneous nephrostomy.

disease of the kidney is suggestive of communication with the pelvicaliceal system and retrograde pyelography is required to confirm the communication. Retrovesical hydatids presenting as bladder outflow obstruction have been reported before (Bahlmann *et al.*, 1986; Kalogeris *et al.*, 1986). In one of the male patients with a pelvic hydatid the diagnosis was delayed because he had a large incisional hernia and the cyst was univesicular and was mistaken repeatedly for a distended urinary bladder on ultrasonography. CT was the most effective diagnostic tool (Shetty *et al.*, 1992) and the specific features have been well documented (Kalogiouris *et al.*, 1986; Hertz *et al.*, 1989; Karabekios *et al.*, 1989). Although Gilsanz *et al.* (1980) reported intrapelvic filling defects on urography in 4 of 5 renal communicating hydatids, none of our patients showed any such feature on IVU. Retrograde pyelography therefore is an essential investigation to delineate such a communication. Eight patients had hydatid cysts of more than one organ, such as the liver, peritoneal cavity and lungs. Multi-organ involvement should be diagnosed by CT pre-operatively, since the surgical approach needs to be carefully chosen. The uraemic patient who underwent surgery had to have a left percutaneous nephrostomy to improve renal function because an attempt at cystoscopy revealed a greatly compressed bladder and the ureteric orifices could not be catheterised. She developed a reno-colo-cutaneous fistula post-operatively following accidental puncture of the grossly dilated splenic flexure. However, the fistula healed spontaneously in the post-operative period.

In approaching renal hydatids we used a supra-twelfth or eleventh rib-bed incision to reach the upper pole. The transperitoneal approach was used in hydatids of multiple organs. Intra-operative scolical agents such as 0.5% silver nitrate or 5%

sodium chloride were used. We also used cryocone in all of the renal and peritoneal hydatids to prevent spillage. In non-communicating renal hydatids, removal of the laminated membrane (endocystectomy) with partial excision of the ectocyst proved successful. No attempt was made completely to excise the ectocyst from the renal substance. However, in 2 communicating hydatids nephrectomy was performed because of the large size of the cysts and the small residual healthy renal cortex. In one patient the ectocyst was closed after removal of the laminated membrane; this was followed by a post-operative leak which eventually ceased with drainage and a double pigtail ureteric stent. If the residual renal parenchyma is substantial, closure of the communication after partial excision of the ectocyst or a partial nephrectomy could be considered (Fig. 2). If the ectocyst is tethered to the diaphragm or undersurface of the liver, it could simply be plicated in non-communicating cysts. The cysts in relation to the urinary bladder were treated by removal of the laminated membrane and drainage. Since these large cysts are densely adherent to the pelvic wall, dissection is hazardous and the cavity can be easily plicated. Patients with pelvic hydatids and renal failure can either undergo double pigtail stenting or percutaneous nephrostomy. If the cyst is large, however, the bladder will be severely compressed and the ureteric orifices may not be visualised. Care should be taken while inserting the nephrostomy and a more posterior tract should be chosen.

The ability of the scolices to develop into mature cysts within the collecting system of the urinary tract or urinary bladder is not known. There are no long-term follow-up studies on the treatment of patients with communicating hydatids. Buckley *et al.* (1985) reported an isolated solitary hydatid cyst within the renal pelvis of a 63-year-old man with

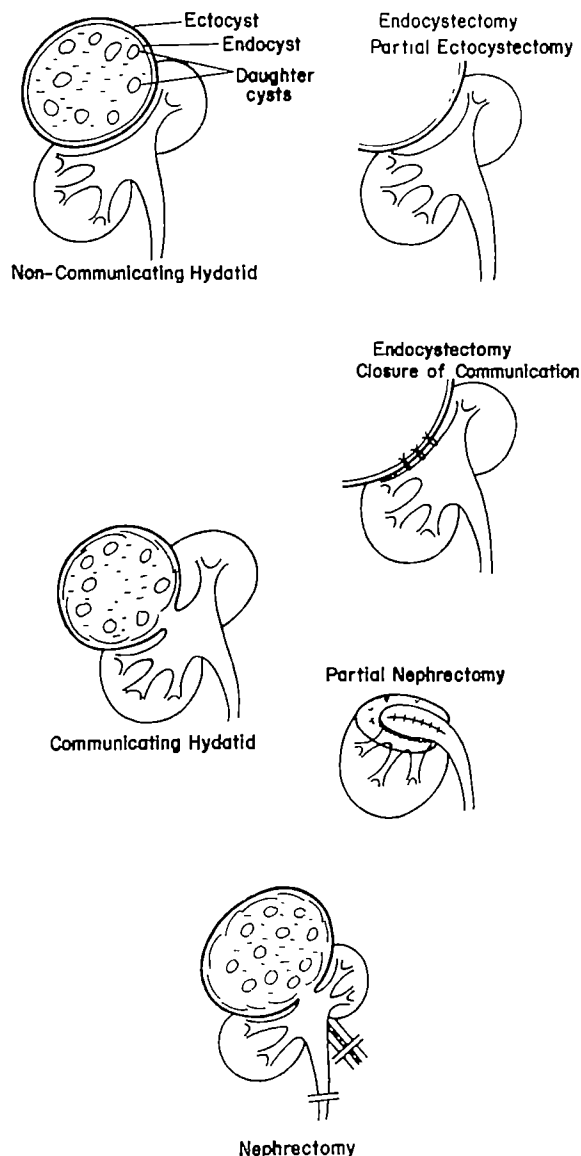


Fig. 2 Surgical treatment options in renal hydatid cyst.

no other focus of hydatid in the kidneys, suggesting that implantation is possible within the urothelium. Post-operative albendazole has been shown to reduce the risk of implantation of scolices (Morris *et al.*, 1985, 1986). Thus albendazole could be used in these patients to prevent implantation. Long-term follow-up is mandatory, especially in the case of communicating renal hydatids.

References

- Al-Ani, M. A. J. and Al-Waili, N. S. (1986) Renal hydatid cysts: report of 15 cases *Saudi Med. J.*, **7**, 478-483.
- Bahlmann, J. C., Richter, Q. and Arndt, T. C. (1986). Echinococcal cyst causing bladder outlet obstruction: a case report. *S. Afr. Med. J.*, **70**, 626-627.
- Benckroun, A., Lakriass, A., Eskalli, N. *et al.* (1986). Hydatid cyst of the kidney. apropos of 30 cases. *J. Urol (Paris)*, **92**, 171-176.
- Buckley, R. J., Smith, S., Herschorn, S. *et al.* (1985). Echinococcal disease of the kidney presenting as a renal filling defect. *J. Urol*, **133**, 660-661.
- Gilsanz, V., Lozano, F., Jr. and Menez, J. (1980) Renal hydatid cyst communication with the collecting system *A.J.R*, **135**, 357-361.
- Halim, A. and Vaezzadeh, K. (1980). Hydatid disease of the urinary tract *Br J Urol.*, **52**, 75-78.
- Hertz, M., Zissin, R., Dresnik, Z. *et al.* (1989) Echinococcus of the urinary tract radiologic findings. *Urol Radiol.*, **6**, 175-181.
- Hossain, A., Bolbol, A. S. and Chaudhury, M. N. H. (1985) Serodiagnosis of human hydatid disease in Riyadh, Saudi Arabia *Ann. Trop. Med. Parasitol.*, **79**, 439-442.
- Kalogeris, K. G., Christoforidis, L. I. and Milloudis, N. M. (1986). Primary retroperitoneal pelvic echinococcal cyst. *J Urol*, **135**, 1235-1236.
- Kalovidouris, A., Pissiotis, C., Pontife, G. *et al.* (1986). CT characterization of multivesicular hydatid cysts. *J. Comput Assist. Tomogr.*, **10**, 428-431.
- Karabekios, S., Goullamos, A., Kalovidouris, A. *et al.* (1989). Features of computed tomography in hydatid cysts of the urinary tract. *Br. J. Urol*, **64**, 575-578.
- Morris, D. L., Chinnery, J. B. and Hardcastle, J. D. (1986). Can albendazole reduce the risk of implantation of spilled protoscolices? An animal study. *Trans. R. Soc. Trop. Med. Hyg.*, **80**, 481-484.
- Morris, A. L., Dykes, P. W., Marriner, S. *et al.* (1985). Albendazole-objective evidence of response in human hydatid disease *J.A.M.A*, **253**, 2053-2057.
- Noah, M. S., Laajam, M. A., Hawass, N. A. *et al.* (1986) Hydatid disease, is it a diagnostic problem? Analysis of 42 consecutive cases in Saudi patients. *Ann Trop. Med. Parasitol*, **80**, 607-614.
- Shetty, S. D., Al-Saigh, A. A., Ibrahim, A. I. A. *et al.* (1992) Hydatid disease of the urinary tract: evaluation of diagnostic methods. *Br J. Urol.*, **69**, 476-480.

The Authors

- S. D. Shetty, MS, FRCSE, FRCS, Assistant Professor of Urology, King Saud University
- A. Al-Saigh, MB,BS, FRCS(I), Assistant Professor of Surgery and Dean, College of Medicine, King Saud University
- A. I. A. Ibrahim, MB,BS, FRCSE, Associate Professor of Urology, King Saud University.
- K. P. Patil, MS, MCh(Urol), Consultant Urologist, Asir Central Hospital.
- C. L. Bhattachan, MB,BS, FRCS, Consultant Surgeon, Asir Central Hospital.

Requests for reprints to: S. D. Shetty, Department of Urology, College of Medicine, King Saud University, P.O. Box 641, Abha, Saudi Arabia.

The Actions of Extracellular Magnesium on Isolated Human Detrusor Muscle Function

B. S. I. MONTGOMERY, P. J. THOMAS and C. H. FRY

Departments of Physiology and Urology, United Medical and Dental Schools of Guy's and St Thomas' Hospitals, London

Summary—The effects of increasing the extracellular magnesium concentration ($[Mg]$) on the *in vitro* mechanical and electrophysiological properties of isolated human detrusor smooth muscle have been investigated. Raising extracellular Mg reduced the magnitude of the electrically-induced phasic contractions as well as spontaneous contractions. A similar increase in the $[Mg]$ reduced the magnitude of the inward Ca^{2+} current associated with the action potential as well as shifting the activation curve to more positive potentials. Spontaneous oscillations of intracellular Ca^{2+} could be observed in some isolated cells and such activity was also abolished by raising the extracellular $[Mg]$.

It is proposed that the contractile effects of raised extracellular Mg are mediated by an action on the inward Ca^{2+} current and that these observations suggest a means whereby normal and abnormal detrusor contractions might be effectively regulated.

Magnesium is an abundant intracellular cation in muscle, although little is known about its action or regulation. Intracellular levels of total Mg in smooth muscle are of the order of 17 mmol/L cell water, although the freely ionised concentration is considerably lower (<1.0 mM) (Fry and Hall, 1989) and in cardiac muscle similar intracellular concentrations of total and freely ionised Mg have been measured. In both muscle types the freely ionised fraction remains remarkably constant despite interventions such as electrical stimulation and ischaemia in smooth muscle (Kushmerick *et al.*, 1986) or large alterations to the concentrations of extracellular ions such as H^+ , Mg^{2+} , Na^+ and K^+ (Fry, 1986). This has led to the suggestion that the observed effects of changing the extracellular $[Mg]$ on muscle function are not mediated by corresponding alterations to the intracellular $[Mg^{2+}]$, but are due to a direct action at the extracellular face of the membrane.

In cardiac muscle a raised extracellular $[Mg]$ reduces muscle excitability and conduction velocity,

as well as exerting a negative inotropic effect (Hall and Fry, 1991; Hall *et al.*, 1991). The electrophysiological actions are mediated via the action potential by a shift of the threshold potential to more depolarised values and an attenuation of the inward currents responsible for the depolarising phase of the action potential. The negative inotropic effect can be explained by an inhibition of the voltage-dependent L-type Ca^{2+} channel.

The actions of extracellular Mg on smooth muscle are less clear. Human detrusor smooth muscle is characterised by a phasic contraction, probably associated with an action potential, as well as smaller changes of resting tension, often of a spontaneous character. The action potential in detrusor muscle is supported by an inward Ca^{2+} current, and repolarisation results from a time-independent K^+ current (Montgomery and Fry, 1991). The origin of spontaneous contractile activity in this tissue is less clear but may be related to generation of spontaneous action potentials or alteration of the ability of intracellular organelles to regulate intracellular Ca^{2+} . Such contractions are increased by hypoxia and decreased by agents

which reduce the phasic contraction and the inward Ca^{2+} current (P. J. Thomas, unpublished data). The relationship between spontaneous mechanical activity and the electrophysiological properties of detrusor muscle in *in vitro* and *in vivo* bladder instability is also unclear, but any manipulation of these *in vitro* properties might result in a reduction of abnormal bladder function. Thus, in the light of the proven actions of extracellular Mg on cardiac muscle it seemed of interest to investigate its action on human detrusor muscle. The results indicate that a raised extracellular [Mg] profoundly reduces stimulated and spontaneous contractions as well as attenuating the inward Ca^{2+} current associated with the action potential. Some of these results have been communicated to the Physiological Society (Montgomery *et al.*, 1991).

Materials and Methods

Preparations

Experiments were performed on either strips of human smooth muscle or individual cells isolated from the smooth muscle mass. Samples of detrusor muscle from the dome and lateral walls of the bladder were obtained by endoscopic cold biopsy or from patients undergoing open operation at St Thomas' and Guy's hospitals. Ethical approval for attainment of such samples had been obtained. Samples were transported immediately to the laboratory in a HEPES-buffered solution made up in ultra-pure water (Milli-Q system, Millipore Corp.), containing no added calcium (pCa 5.7) and maintained at pH 7.2. The solution contained (mM): NaCl 110, NaHCO_3 23, KCl 4.0, MgCl_2 1.0, NaH_2PO_4 0.4, HEPES 20, glucose 6.0, Na pyruvate 5.0, and titrated with 1M NaOH. The mucosa was dissected from the preparation and the remaining smooth muscle used either for the preparation of isolated cells or muscle strips.

Tension recording

Strips of muscle, approximately 2 mm long and <0.5 mm diameter, were cut from the biopsy specimen and mounted horizontally in a superfusion trough. The strip was tied at one end to a fixed hook embedded in the floor of the trough and at the other end to an isometric force transducer (UC2, Statham, Oxnard, USA). The preparation was superfused with a Tyrode solution containing (mM): NaCl 118, NaHCO_3 24, KCl 4.0, MgCl_2 1.0, NaH_2PO_4 0.4, CaCl_2 1.8, glucose 6.0, Na pyruvate 5.0. The solution was pre-heated and

maintained at 36°C and equilibrated with a 95% O_2 /5% CO_2 gas mixture to give a pH of 7.33 ± 0.02 . The preparation was field stimulated with platinum electrodes embedded in the wall of the trough. Square 0.2 ms pulses were delivered in 20 Hz, 4 s trains at 90 s intervals. This mode of stimulation elicited a contraction due to excitation of the cholinergic nervous network embedded in the muscle (Palfrey *et al.*, 1984). The output of the isometric force transducer was displayed on a moving-paper chart recorder (2400S, Gould Instruments, Hainault, Essex).

Single-cell isolation

Isolated cells were prepared from small pieces of the cleaned biopsy specimen by initially storing them overnight at 4°C in a 50:50 solution of HEPES buffer and a disaggregation solution. The disaggregation solution consisted of the following components added to HEPES buffer: 0.2% collagenase (Worthington Biochemical Corp., USA; 219 u/mg), 0.1% trypsin inhibitor type II-S, 0.05% hyaluronidase type III, 0.05% hyaluronidase type I, 0.5% fatty acid free BSA (all from Sigma Chemical Co. Ltd, Poole). The pCa of the disaggregation solution was 4.3. The tissue was washed in HEPES buffer at 37°C, incubated with disaggregation solution for 20 min, washed again several times and then dissociated by gentle trituration with an unsilanised glass pipette. Cells thus prepared remained viable for up to 12 h.

Electrophysiological measurements

Experiments were performed in a water-jacketted Perspex chamber (volume 250 μl , temperature 36°C), the base of which was a glass cover-slip. The chamber was placed on the stage of an inverted-stage microscope (Zeiss IM) with $\times 320$ magnification. A small sample of the cell preparation was placed in the chamber, left for about 30 min to adhere to the base and then superfused with Tyrode solution. The [Mg] of the Tyrode solution was changed by adding samples of a 1.0 M stock solution to Tyrode solution; no osmotic correction was made.

Ionic currents were recorded using a single patch-electrode (2–5 M Ω) in the whole-cell configuration, filled with a caesium-containing solution to block outward currents. The filling solution contained (mM): CsCl 130, glucose 11.5, HEPES 6.0, TEA 5.0, ATP 3.0, MgCl_2 2.9, EGTA 1.0 (Klöckner and Isenberg, 1985). Voltage-clamp protocols were determined by a CED software package (CED Ltd, Cambridge) with stimulation and recording per-

formed via an Axopatch-1C (Axon Instruments, Oxnard, USA). Membrane current data were filtered at 2 kHz by the Axopatch-1C, and current and voltage were sampled at 4 kHz during A-D conversion (CED 1401, Cambridge). Current and voltage signals were digitised using a CED 1401 and stored on-line to a microcomputer (Dell Corp., System 200) with 4 Mb of RAM and a 20 Mb hard disk. Data were backed-up to $\frac{1}{4}$ " tape and could subsequently be analysed off-line. Capacitative artefacts and series resistance were compensated with the Axopatch-1C and regularly reviewed during an experiment.

Data and statistical analyses were performed on a Macintosh SE microcomputer; data were stored as text files and transferred using 5 $\frac{1}{4}$ " discs and MacLink Plus™ (DataVis Inc., USA) software to transfer the text files. Statistical analysis used 1-tailed paired Student's *t* tests; values quoted refer to the mean from a given number of cells $\pm$ 1 standard deviation.

Estimates of the intracellular $[Ca^{2+}]$

Qualitative changes to the intracellular $[Ca^{2+}]$ were measured using epifluorescence microscopy. Cells were incubated with 5 μ M of the fluorochrome Fura-2 AM (Molecular Probes Inc., Eugene, USA) for approximately 20 min before being placed in a water-jacketed chamber (36°C) and allowed to

adhere to the glass base before superfusion with Tyrode solution was commenced. All experiments were performed on the stage of an inverted microscope (Nikon Diaphot, Halesfield). The loaded cells were alternately excited at 340 and 380 nm at a rate of 20/s and emitted light between 410 and 500 nm collected by a system synchronised to the rate of alternation of the excitation filters (Cairn Instruments, Sandwich). The ratio of emitted light when excited at 340 and 380 nm was displayed as an analogue signal on a moving-paper chart recorder (2400S, Gould Instruments, Hainault); an increase of the ratio was interpreted as a rise of the $[Ca^{2+}]$.

Results

Phasic contractile function

The effect of raising the extracellular $[Mg]$ on the contractile properties of detrusor muscle is illustrated in Figure 1A. Electrical stimulation results in a transient contraction, superimposed on a small level of spontaneous activity in this preparation. An increase of the superfusate $[MgCl_2]$ from 1 to 5 mM depressed the magnitude of the phasic contraction, reduced base-line tension and abolished spontaneous activity. These changes were fully reversible upon return to control solution.

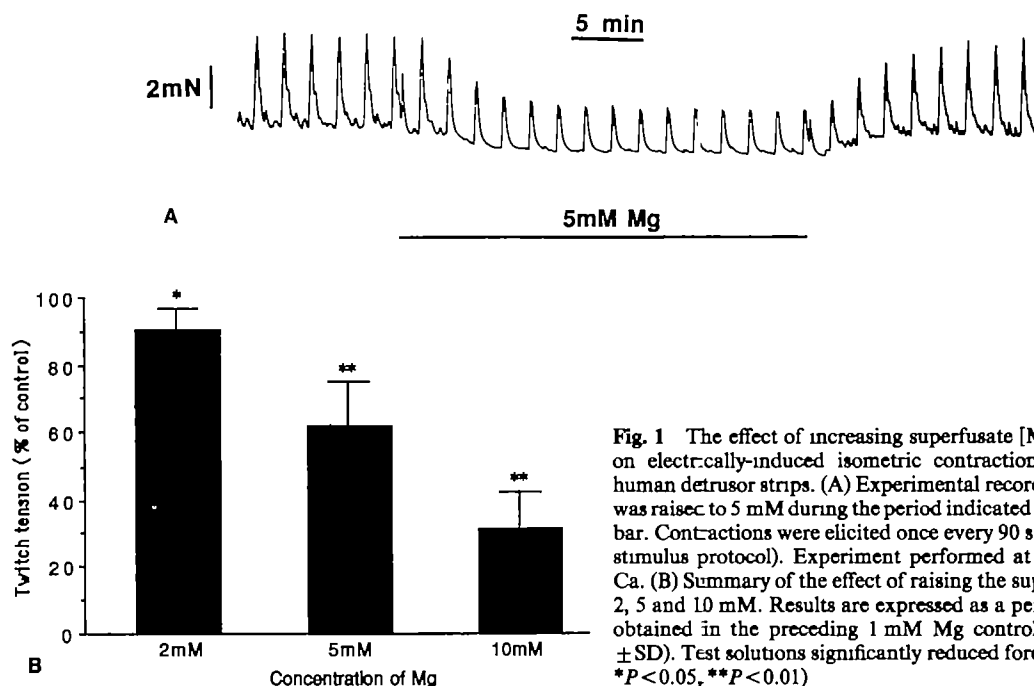


Fig. 1 The effect of increasing superfusate $[Mg]$ above 1 mM on electrically-induced isometric contractions from isolated human detrusor strips. (A) Experimental recordings as the $[Mg]$ was raised to 5 mM during the period indicated by the horizontal bar. Contractions were elicited once every 90 s (see *Methods* for stimulus protocol). Experiment performed at 36.5°C, 1.8 mM Ca. (B) Summary of the effect of raising the superfusate $[Mg]$ to 2, 5 and 10 mM. Results are expressed as a percentage of force obtained in the preceding 1 mM Mg control solution ($n=5$, $\pm$ SD). Test solutions significantly reduced force (1-tailed *t* test, * $P < 0.05$, ** $P < 0.01$)

The dose-dependent effects of the extracellular [Mg] on phasic contraction strength are summarised in Figure 1B. Increasing the [Mg] from 1 to 10 mM resulted in a progressive decline of force, such that in 2 mM, 5 mM and 10 mM MgCl_2 solution, force had declined to $90.6 \pm 6.5\%$, $61.6 \pm 13.4\%$ and $31.0 \pm 11.3\%$ (SD of an observation, $n=5$), respectively, of control. It was difficult to quantify the fall of resting tension or reduction of spontaneous activity in raised [Mg] solutions. However, in all preparations an increase to ≥ 5 mM abolished spontaneous activity, when it was present under control conditions, and resting tension progressively declined as the superfusate [Mg] was sequentially raised between 1 and 10 mM. In all cases the effects were fully reversible upon return to the control solution.

A raised extracellular [Mg] has been shown to depress neuromuscular transmission by attenuating transmitter release from presynaptic terminals (del Castillo and Katz, 1954). The stimulation protocol used in this preparation has been shown to elicit contraction by stimulating cholinergic nerves embedded in the smooth muscle mass (Palfrey *et al.*, 1984) and it was possible that the effect of raising the [Mg] did not directly affect the smooth muscle membrane but reduced acetylcholine release. Therefore, the effects of an elevated [Mg] on isometric twitches elicited by direct muscle stimulation were investigated. Nerve-mediated transmission was blocked by the addition of TTX (10^{-7} g/ml) and atropine (1 μM) to the superfusate and the muscle stimulated directly by increasing the pulse-width of the stimulus (>1 ms). The effects of

elevated [Mg] on contractile force induced by direct muscle stimulation were quantitatively similar to those obtained via nerve-mediated stimulation, as in Figure 1. Thus it may be concluded that increased levels of extracellular Mg reduce the contractility of isolated human detrusor strips via a direct action on the smooth muscle.

Inward Ca^{2+} current i_{Ca}

The inward current responsible for the upstroke of the action potential has been shown to be carried by Ca^{2+} in both animal and human detrusor muscle (Klöckner and Isenberg, 1985; Montgomery and Fry, 1991) and a strong association between the strength of phasic contractile force and the magnitude of i_{Ca} has been demonstrated during several inotropic interventions. The inward current was measured in isolated detrusor cells during superfusion with 1 and 10 mM Mg Tyrode solutions. Figure 2 shows superimposed current traces obtained from the same cell in normal and raised Mg solutions when the membrane potential was stepped from -60 to 0 mV for 100 ms. Records were obtained with CsCl-filled patch electrodes to block outward currents so that the net current at the end of the clamp step showed no outward component. The peak inward current magnitude was attenuated in 10 mM Mg Tyrode and the effect could be shown to be completely reversible upon return to control. In 7 cells i_{Ca} was reduced to $43 \pm 18\%$ of control in raised [Mg] Tyrode. The effect was attained within 30 s of the solution change, which is similar to the exchange time of the fluid within the superfusion system as assessed by placing a thermistor in the

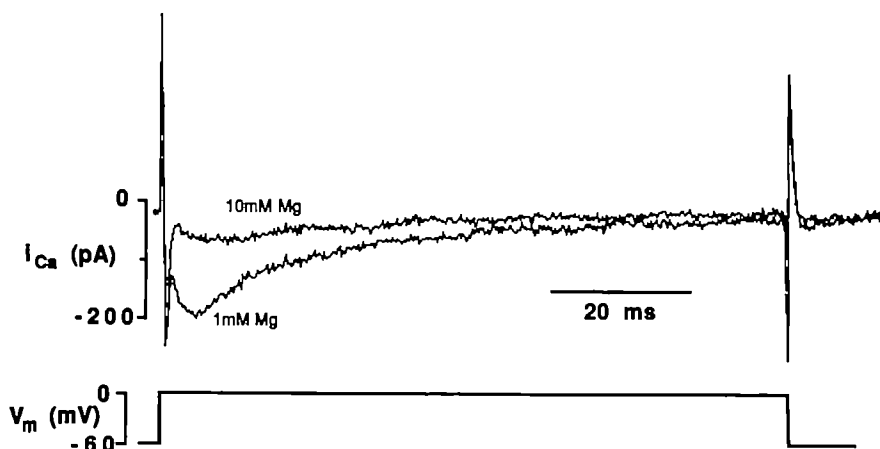


Fig. 2 The effect of increasing the extracellular [Mg] from 1 to 10 mM on the inward Ca^{2+} current, i_{Ca} . Currents were recorded with a CsCl-filled electrode to abolish outward currents. Experiment performed at 36.5°C , 1.8 mM Ca.

chamber and using 2 solutions of different temperatures. Thus the effect of Mg^{2+} is likely to be extracellular rather than due to a secondary change of the intracellular $[Mg^{2+}]$.

The reduction of i_{Ca} in raised Mg solutions with the above protocol may result not from an attenuation of the current but a shift of the current-voltage relationship to more positive potentials, so that the current was less fully activated. Therefore, the effect of $[Mg]$ on the current-voltage relationship (CVR) of i_{Ca} was investigated. Figure 3A shows that over the range of potentials -20 mV to $+10$ mV the magnitude of i_{Ca} was significantly reduced in 10 mM $MgCl_2$ (closed circles) compared with that in 1 mM $MgCl_2$ (open circles); at other clamp potentials, scatter of the data precluded the demonstration of a significant difference in the 2 solutions.

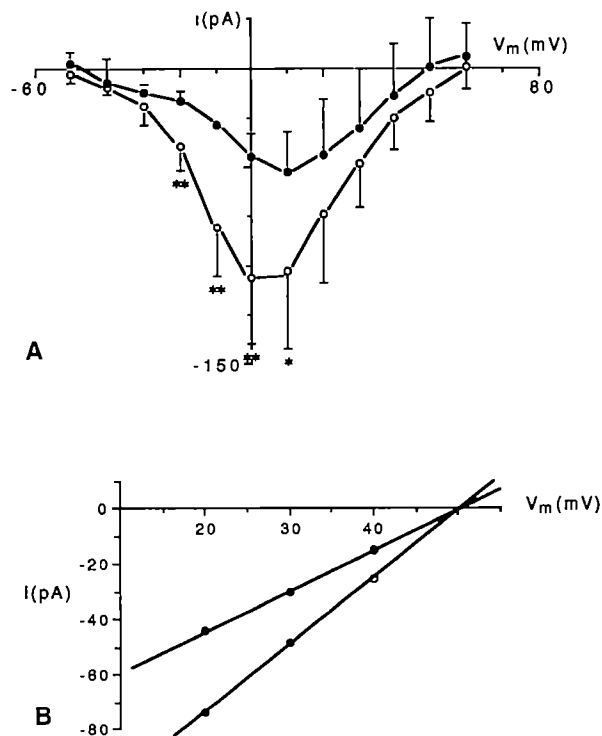


Fig. 3 Current-voltage relationships (CVRs) of the inward Ca^{2+} current, i_{Ca} , in 1 and 10 mM Mg ($\circ$ and $\bullet$, respectively). (A) Entire CVRs, recorded with CsCl-filled electrodes (1-tailed t test, $*P < 0.05$, $**P < 0.01$). (B) The determination of E_{rev} in 1 and 10 mM Mg by extrapolation of the line, obtained from a least-squares fit, to the mean data points taken from the respective mean CVRs between $+20$ and $+40$ mV. ($\circ E_{rev} = 52$ mV, slope = 2.4, $r^2 = 0.99$, $\bullet E_{rev} = 52$ mV, slope = 1.5, $r^2 = 0.99$).

No change of the reversal potential, E_{rev} , of i_{Ca} was observed in the 2 solutions. Figure 3B shows part of the CVRs at clamp potentials $+20$ to $+40$ mV from which the value of E_{rev} was determined from extrapolation of the linear relationship fitted to these data points. In both solutions the value of E_{rev} was $+52$ mV ($+52 \pm 3.5$ mV, 1 mM Mg; $+52 \pm 4.3$ mV, 10 mM Mg). The slope of the CVR at positive potentials permitted calculation of the maximal membrane Ca^{2+} conductance (g_{Ca}). In 1 mM and 10 mM Mg the values were 2.4 ± 0.7 nS and 1.4 ± 0.7 nS respectively (SD of an observation, $n = 4$, $P < 0.05$).

The CVRs in Figure 3A show that maximal current was obtained at a more positive potential, suggesting that the activation curve may be shifted in this direction. Figure 4 shows activation curves of i_{Ca} measured in 1 and 10 mM Mg (open and closed circles respectively) in which Ca^{2+} conductance, g_{Ca} , as a proportion of g_{Ca} , is plotted as a function of voltage. In raised Mg solutions the curve is shifted to more positive potentials. In 4 cells the value of $V_{0.5}$, the voltage at which g_{Ca} is half maximal, was significantly shifted from -13 ± 4 mV to 0 ± 8 mV (SD of an observation, $n = 4$, $P < 0.05$).

It has been demonstrated that the upstroke of the detrusor action potential is carried by Ca^{2+} , and that an attenuation of the inward Ca^{2+} current, i_{Ca} , is associated with a reduced upstroke velocity and a decrease of the excitability of the cell (Montgomery *et al.*, 1991). In normal Tyrode solution (1 mM

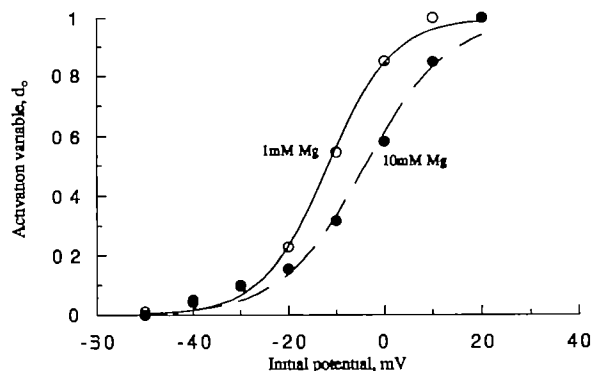


Fig. 4 The effect of increasing the $[Mg]$ from 1 to 10 mM ($\circ$ and $\bullet$, respectively) on the relationship between Ca^{2+} conductance g_{Ca} , expressed as a percentage of the maximum conductance g_{Ca} , and initial membrane potential, V_m . The curves were fitted by a least-squares programme using the mean values of $V_{0.5}$ found for individual cells (-13 and 0 mV in 1 and 10 mM Mg, respectively).

Mg), action potentials were elicited with a depolarising current pulse, recorded with CsCl-filled electrodes, with upstroke velocity of $2.5 \pm 1.0 \text{ V.s}^{-1}$ ($n=7$). In 10 mM Mg Tyrode, action potentials failed to develop, even following an increase of the depolarising current pulse to supra-maximal levels.

Spontaneous contractile activity

Figure 1 shows that increasing the extracellular [Mg] not only reduced the magnitude of phasic contractile activity but also reduced resting baseline tension and abolished the small spontaneous contractions. The origin of the spontaneous contractions and the influence of extracellular Mg were further investigated in isolated detrusor cells loaded with the fluorescent Ca^{2+} indicator, Fura-2. Figure 5 shows an example of the fluorescence emission from a cell which showed spontaneous fluctuations in normal Tyrode solution. An upward deflection indicates an increase of the free intracellular $[\text{Ca}^{2+}]$, although the scale is uncalibrated in terms of absolute Ca^{2+} concentrations. An increase of the extracellular [Mg] from 1 to 5 mM abolished the spontaneous phasic rises of intracellular Ca^{2+} as well as reducing the resting level. The changes were fully reversible on re-admission of normal Tyrode solution. Such spontaneous changes to the intracellular $[\text{Ca}^{2+}]$ were not observed in the majority of cells. However, when they were evident they could always be abolished by increasing the extracellular [Mg].

Discussion

The data show that raising the extracellular [Mg] can have marked effects upon the electrophysiological and contractile properties of human detrusor

muscle. In this preparation the phasic contraction elicited by tetanic trains of short pulses has been shown to be mediated by the cholinergic nervous network embedded in the tissue mass (Palfrey *et al.*, 1984), which elicits an action potential on the muscle membrane. The inward current responsible for the rising phase of the action potential has been shown to be carried by Ca^{2+} , and the magnitude of this Ca^{2+} current, i_{Ca} , will influence directly the contractile state of the tissue. With various extracellular interventions, such as altering pH and the $[\text{Ca}]$, a nearly proportional relationship between the magnitude of i_{Ca} and the force of contraction has been described (Montgomery *et al.*, 1991). The above data are consistent with this scheme as a 10-fold increase of the extracellular [Mg] depressed contractile force by $31 \pm 11\%$ and the magnitude of i_{Ca} by $43 \pm 18\%$. It would appear, therefore, that in this tissue a simple and direct relationship exists between voltage-dependent transmembrane movements of Ca^{2+} and the contractile state. This would have profound implications for the control of detrusor contractility by agents which affect the magnitude of i_{Ca} .

It is also observed that the excitability of the tissue was reduced by an increase of the extracellular [Mg] from 1 to 10 mM, as it was observed that using constant-current stimulation, action potentials failed to be elicited under these conditions. The reasons for reduced excitability in tissue could result from a hyperpolarisation of the resting potential or a shift of the threshold potential to more positive values. Both of these phenomena would increase the amount of current required to shift the resting membrane potential from the normal to a threshold value. The evidence from the above data indicates that a raised extracellular [Mg] shifts the threshold to more positive values. The activation curve of the inward Ca^{2+} current, which is responsible for the rising phase of the action potential, was shifted by some 13 mV to a more positive value, whilst it was observed that the holding current required to maintain a given resting potential during voltage-clamp experiments was unaltered, indicating no change to the resting membrane potential under normal conditions.

The experiments presented above indicate that a raised [Mg] acts directly on the smooth muscle rather than by influencing the efficiency of neuromuscular transmission. A raised [Mg] has been shown to reduce cholinergic transmission at the neuromuscular junction by attenuating the presynaptic release of acetylcholine (del Castillo and Katz, 1954). In these studies, however, identical results

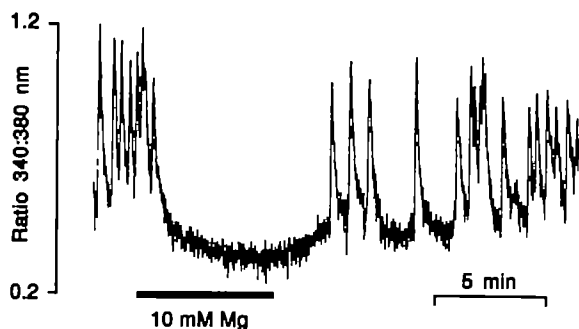


Fig. 5 The effects of 10 mM Mg on the spontaneous, transient increases of intracellular $[\text{Ca}^{2+}]$ observed in an isolated human detrusor muscle cell loaded with Fura-2. Experiment performed at 36°C , 1.8 mM Ca .

with the multicellular preparations were obtained if the muscle preparations were stimulated via the attendant nerve network, using short-duration pulses, or directly using longer pulses and blocking the nervous elements with tetrodotoxin and atropine. Moreover, the fact that extracellular Mg exerted effects on isolated cells also implied a direct action on the muscle cell.

Spontaneous contractile activity has been observed in a number of isolated multicellular animal preparations (Sibley, 1984), although its presence in human preparations is more unusual (Palfrey *et al.*, 1984). In human preparations the magnitude and frequency of such contractions is accentuated by hypoxia (P. J. Thomas, unpublished data) and reduced by interventions which attenuate the phasic contraction and inward Ca^{2+} current. Therefore, it might be proposed that such contractions arise when the intracellular calcium content is high. Similar observations have been made in cardiac muscle when intracellular calcium has been raised by application of cardiac glycosides (Allen *et al.*, 1984). Under these conditions there is spontaneous release of Ca^{2+} from the sarcoplasmic reticulum, as well as secondary depolarisations after the action potential which, if large enough, can lead to the induction of further action potentials. If a similar situation existed in this tissue an increase of the extracellular [Mg] would attenuate such secondary action potentials by attenuating the inward Ca^{2+} current.

Such observations suggest a possible avenue for the action of potentially useful therapeutic agents on controlling detrusor muscle function. Manipulation of the voltage-dependent inward Ca^{2+} current has been shown *in vitro* to depress both electrically stimulated and spontaneous contractions, and it would be useful to ascertain whether such possibilities also exist in the intact bladder.

Acknowledgements

We are grateful to the Trustees of St Thomas' Hospital and the Medical Research Council for financial assistance, as well as the surgical staff of St Thomas' and Guy's hospitals for obtaining tissue samples.

References

- Allen, D. A., Elmer, D. A. and Orchard, C. H. (1984). Characterisation of oscillations of intracellular calcium concentration in ferret ventricular muscle. *J. Physiol.*, **352**, 113–128.
- del Castillo, J. and Katz, B. (1954). The effect of magnesium on the activity of motor nerve endings. *J. Physiol.*, **124**, 553–559.
- Fry, C. H. (1986). Measurement and control of intracellular magnesium ion concentration in guinea-pig and ferret ventricular myocardium. *Magnesium*, **5**, 306–316.
- Fry, C. H. and Hall, S. K. (1989). The role of magnesium in the regulation of muscle function. In *Metal Ions in Biological Systems*, ed. Sigel, H. and Sigel, A. Volume 26. pp 463–488. New York, Basel: Marcel Dekker.
- Hall, S. E. and Fry, C. H. (1991). The effects of extracellular Mg on excitation of isolated ventricular myocardium from rat, rabbit and ferret. *J. Physiol.*, **429**, 24P.
- Hall, S. E., Fry, C. H. and MacLeod, K. T. (1991). The effect of extracellular Mg on the contraction of isolated ventricular myocardium from several mammalian species. *J. Physiol.*, **429**, 23P.
- Klöckner, U. and Isenberg, G. (1985). Action potentials and net membrane currents of isolated smooth muscle cells (urinary bladder of the guinea-pig). *Pflügers Arch.*, **405**, 329–339.
- Kushmerick, M. J., Dillon, P. F., Meyer, R. A. *et al.* (1986). ^{31}P -NMR spectroscopy, chemical analysis and free Mg^{2+} of rabbit bladder and uterine smooth muscle. *J. Biol. Chem.*, **261**, 14420–14429.
- Montgomery, B. S. I. and Fry, C. H. (1991). The ionic basis of the action potential in isolated human detrusor muscle. *J. Urol.* (In press).
- Montgomery, B. S. I., Thomas, P. J. and Fry, C. H. (1991). The actions of extracellular Mg on isolated human detrusor muscle. *J. Physiol.* (In press).
- Palfrey, E. L. H., Fry, C. H. and Shuttleworth, K. E. D. (1984). A new *in vitro* perfusion method for the investigation of human detrusor muscle. *Br. J. Urol.*, **56**, 635–640.
- Sibley, G. N. A. (1984). A comparison of spontaneous and nerve-mediated activity in bladder muscle from man, pig and rabbit. *J. Physiol.*, **354**, 431–443.

The Authors

- B. S. I. Montgomery, BSc, FRCS, Research Registrar, St Thomas' Hospital.
- P. J. Thomas, FRCS, Senior Registrar, Guy's Hospital.
- C. H. Fry, BSc, BA, PhD, Reader in Cell Physiology, London University.

Requests for reprints to: C. H. Fry, Department of Physiology, UMDS (St Thomas' Hospital Campus), Lambeth Palace Road, London SE1 7EH.

Vesica Fellea—A New Substitute for the Bladder?

An Experimental Study

T. GÜÇER and H. OZKARDES

Department of Plastic and Reconstructive Surgery, Hacettepe University; Urology Clinic, Ankara Hospital, Ankara, Turkey

Summary—The urinary bladders of 8 dogs were removed and replaced with their own gallbladders using microvascular anastomoses. Post-operative assessment included measurement of blood urea nitrogen (BUN) and creatinine (Cr), intravenous urography and histological examination of the autotransplanted gallbladders.

The neobladders proved to be good reservoirs without urinary leakage. Renal function was well preserved in 6 dogs; post-operative BUN and Cr levels were raised in 2 dogs and the concentrating ability of the kidneys was reduced. The neobladders were perfect histologically.

There is no doubt that radical or total cystectomy with urinary diversion has a place in the treatment of patients with severe congenital anomalies and tumours of the urinary bladder (Hendren, 1976).

The undesirable complications of urinary diversion are well known (Richie, 1986) and low pressure bladder substitutes are receiving increasing attention (Alcini *et al.*, 1989; Studer *et al.*, 1989).

This experimental study was a preliminary trial to assess the feasibility of using the gallbladder as a substitute for the urinary bladder.

Materials and Methods

Experiments were done in 8 female dogs with body weights of 17.5 to 23.5 kg. Under intratracheal general anaesthesia with sodium pentobarbital, the abdominal cavity was entered through a midline incision. A modified classical cholecystectomy was performed, preserving the main artery and vascular arborisation of the organ. After resection the gallbladder was emptied, irrigated with cold saline, which also served to estimate the approximate capacity of the resected organ, and stored in a cool place after its vascular pedicle was defined and secured with a fine stay suture. The second step was a simple cystectomy. The ureters were transected

just above the vesicoureteric junctions and secured without torsion, by traction sutures. At least one suitably sized branch of the hypogastric artery was preserved for later anastomosis. The urethra was dilated antegradely to decrease outlet resistance.

The gallbladder was orthotopically autotransplanted into the pelvis and a microvascular end-to-end or end-to-side arterial anastomosis was done between the cystic artery and a formerly vesical branch of the hypogastric artery. Unlike human beings, the venous return from the gallbladder in dogs is mainly via the liver, and for this reason we frequently had difficulty in finding a vein suitable for direct venous anastomosis. This problem was solved by not making a venous anastomosis; instead the dog was anticoagulated with 100 iu/kg subcutaneous heparin and a drain was left around the neobladder draining the venous blood that poured out from the rough surface until neovascularisation took place.

After the vascular anastomosis was completed the ureters were reimplanted into the gallbladder using 2 techniques. One was a direct anastomosis without a non-refluxing technique and the other a non-refluxing type of anastomosis in which a short segment of distal ureter was left free in the neobladder. The cystic stoma was spatulated before the cystourethral anastomosis to approximate the 2 structures properly. The vascular pedicle was

carefully preserved during all non-vascular anastomoses. Finally, the neobladder was wrapped in omental tissue and drained with a Foley urethral and two 3F ureteric catheters. All catheters were removed on the second post-operative day and a free flow of urine from the overdilated urethra was observed. The blood urea nitrogen (BUN) and creatinine (Cr) levels were determined on every other day after the first.

On the seventh post-operative day intravenous urograms (IVU) were obtained using 1 ml/kg (300 mg iodine/kg body weight) iohexol. On the fifteenth post-operative day the animals were sacrificed and before being examined histologically the neobladder capacities were measured again by filling them with water under gravity.

Results

IVU findings on the seventh day showed a marked decrease in the concentrating ability of the kidneys of the 2 dogs in which vesicoureteric continuity had been obtained by direct anastomosis, and was probably caused by the effect of the rising intravesical pressures on the upper collecting system. In all cases the neobladder wall was intact and there was no leakage of urine radiologically.

Second-look operations on the fifteenth post-operative day revealed that the peritoneal surface of the neobladders was still separate from the surrounding tissues, but the rough surface which had been dissected from the liver was supported by the adhesion of adjacent intestine or omental tissue, providing the organ with an additional vascular supply. The mean volume of the resected gallbladders was 36 ml (range 30–45), but after 15 days the expected increase in capacity was not very marked and rose only to 42 ml (range 30–51). Histopathological examination of the neobladders showed only minimal inflammatory changes.

Discussion

Intestinal conduits or bladder substitutes have always carried the risk of obstruction and absorption sufficient to cause serious metabolic changes, although the long-term results of low pressure ileal bladder substitutes seem promising (Studer *et al.*, 1989).

Intestinal structures have always attracted surgeons interested in urological reconstruction. The first and, to our knowledge, the only experiment which created a relationship between the biliary and urinary systems was the experience of Kapsi-

now *et al.* (1924), who performed cholecystonephrostomies in dogs for internal biliary drainage.

The gallbladder has a storage function similar to that of the urinary bladder, but its contractility is weaker. The storage function of the gallbladder was exploited in the present experiments and proved to be effective. The volume ratio of gallbladder to urinary bladder is approximately 1:2 in dogs (30–40 ml to 60–80 ml) and 1:4 in man (90 ml to 400 ml), but we do not consider this difference to be a major drawback to the application of this technique in patients, since urine itself can expand the neobladder, which is known to be very compliant. Even in the 15-day period of these experiments the volume of the gallbladder increased from a mean of 36 ml to a mean of 42 ml (17%). We tried to perform filling cystometrograms in these dogs but were unsuccessful in obtaining reliable data. This aspect requires further assessment.

The contractility of the transplanted gallbladder was not tested in the present study, but providing the neobladder is viable and receives sufficient blood it should respond to circulating hormones such as cholecystokinin.

We believe that the results of replacing the urinary bladder with the gallbladder are promising.

Acknowledgements

We are grateful to Dr Güler Gürsu, Chairman and Professor of Plastic and Reconstructive Surgery at Hacettepe University, for her invaluable scientific and moral help throughout this study.

References

- Alcini, E., Grassetti, F., D'Addessi, A. *et al.* (1989). Bladder replacement by ileocaeco-urethrostomy or ileo-urethrostomy with a reservoir after cystoprostate-vesiculectomy for bladder cancer. *Br. J. Urol.*, **63**, 36–42.
- Hendren, W. H. (1976) Exstrophy of the bladder: an alternative method of management. *J. Urol.*, **115**, 195–202.
- Kapsinow, R., Engle, L. P. and Harvey, S. C. (1924). Intraabdominal biliary exclusion from the intestines. cholecyst-nephrostomy, a new method. *Surg. Gynecol. Obstet.*, **39**, 62–65.
- Richie, J. P. (1986). Complications of urinary diversion. In *Urologic Complications, Medical and Surgical, Adult and Pediatric*, ed. Marshall F. F. Chapter 16, pp. 213–223. Chicago: Year Book Medical Publishers.
- Studer, U. E., Ackermann, D., Casanova, G. A. *et al.* (1989). Three years' experience with an ileal low pressure bladder substitute. *Br. J. Urol.*, **63**, 43–52.

The Authors

T. Güçer, MD, Chief Resident, Department of Plastic and Reconstructive Surgery, Hacettepe University.
H. Özkardeş, MD, Urologist, Ankara Hospital.

Requests for reprints to: H. Özkardeş, S.B. Ankara Hospital, Üroloji Kliniği, 06340 Ankara, Turkey

Outcome in Carcinoma *in situ* of Bladder Treated with Intravesical Bacille Calmette-Guérin

S. J. HARLAND, C. R. CHARIG, W. HIGHMAN, M. C. PARKINSON and P. R. RIDDLE

St Peter's Hospital and Institute of Urology, London

Summary—Fifty-three patients with carcinoma *in situ* of the bladder were treated with Evans strain BCG given intravesically. Complete remission was achieved after either one or two 6-weekly courses in 53% of patients. The median duration of remission was 32 months. Treatment-related bladder symptoms were minor during the first course, more severe during the second. There was no relation between severity of symptoms and likelihood of response. With a median follow-up of 32 months, disease progression has occurred in 10% of complete responders, whereas failure to respond on either cystoscopic, histological or cytological grounds was associated with a 48% progression rate. Although intravesical BCG produces impressive responses in carcinoma *in situ* of the bladder, managed conservatively the condition remains a dangerous one.

It is now well established that intravesical BCG can normalise the malignant transitional epithelium in flat carcinoma *in situ* (CIS) of bladder (Reitsma *et al.*, 1989). Uncertainty remains relating to the strain of BCG, the concentration used and the duration of therapy. Furthermore, although BCG therapy has been frequently successful, CIS of bladder remains a dangerous condition when managed conservatively. For example, in his series of 48 such patients treated with BCG, Brosman (1989) described 18 who died of transitional cell carcinoma of bladder.

We describe our early experience with 53 patients with carcinoma *in situ* treated with the Evans strain of BCG in a dose significantly lower than has been described elsewhere (Cumming *et al.*, 1989).

Patients and Methods

The diagnosis of flat carcinoma *in situ* was made in all patients on the basis of positive urine cytology together with the characteristic appearance of CIS (Riddle *et al.*, 1976). Positive cytology alone was accepted as diagnostic of CIS in patients whose

bladder biopsies were denuded of epithelium. Included in this series were patients whose CIS was associated with previous or concurrent superficial (pTa and pT1) papillary disease. Either initial diagnosis of CIS or review was carried out in each patient by the same pathologist. An assessment was made of the extent of disease within the bladder based on the referring surgeon's description and, where several had been performed, the proportion of random biopsies (usually 4) which were positive.

The treatment consisted of 16 ampoules of Evans (formerly Glaxo) BCG ($0.8\text{--}2.4 \times 10^9$ total viable organisms) mixed with 50 ml of normal saline and instilled intravesically weekly $\times 6$. No treatment course was started less than 4 weeks following the previous cystoscopy. Assessment was carried out not less than 4 weeks after the last instillation by cystoscopy and biopsies, and urine cytology. If CIS was again found in the bladder a further course of BCG was given.

After each treatment a careful assessment of toxicity was made, with maximal bladder symptoms being scored on a 0–3 scale for each of frequency, dysuria, nocturia and haematuria. From the weekly symptom score was subtracted the symptom score pre-treatment. Similarly, a urinary white cell count was scored each week prior to treatment.

Follow-up was timed from the start of BCG

therapy. Complete remission (CR) was defined as normalisation of the intact transitional epithelium on bladder biopsy with negative urine cytology. The duration of CR was timed from the end of the last BCG instillation prior to the "clear" cystoscopy. The frequency of cystoscopic follow-up was at the referring surgeon's discretion. Urine cytology was performed every 3 to 6 months.

Relapse was defined as the occurrence, following CR, of transitional cell carcinoma (TCC)—any stage—or of positive urine cytology. Progression was defined as the development of TCC invasive of muscle or prostatic stroma, or the development of metastatic disease.

The statistical significance of differences between proportions was assessed using the chi-squared test.

Table 1 Details of Patients

Total no	53
Male/female	44/9
Median age (years) (range)	71 (43–91)
CIS-related bladder symptoms (%)	32 (60)
Over 50% of bladder involved (%)	33 (62)
No history of exophytic disease (%)	18 (34)
Previous (only) exophytic disease* (%)	15 (28)
Concurrent exophytic disease (%)	20 (38)
pTa/pT1	4/16
G2/G3	12/8
Positive urine cytology (%)	53 (100)
Median follow-up in months (range)	32 (12–51)

* Histology not reviewed

Results

The patients' characteristics are shown in Table 1. All patients had positive urine cytology. In none of 6 patients referred with a histological diagnosis of CIS and consistently negative urine cytology was the diagnosis upheld on slide review.

Complete remission

Nineteen patients (36%) attained CR after their first course of BCG. Of 22 patients receiving a second course, 9 (41%) became disease-free, giving an overall CR rate of 53%. Twelve patients who failed on the first course had no second course. The reasons for this were the presence of muscle-invasive disease at first follow-up cystoscopy (3), negative bladder biopsies with positive urine cytology (4), resolution of CIS but persistent exophytic disease (2), severity of BCG cystitis (1) and frailty (1). The median duration of CR was 32 months (Fig.).

Pre-treatment characteristics and response

Neither the presence of CIS-related bladder symptoms, nor the presence or absence of a history of exophytic disease influenced the response rate to BCG (Table 2a). There was a trend of borderline significance for a favourable response to treatment when the disease involved less than 50% of the bladder surface.

Table 2 Disease-related Features, Response to Intravesical BCG and Disease Progression

(a) Response		Success rate		
Risk factor		Present (%)	Absent (%)	
Cis-related bladder symptoms: 1st course		12/32 (36)	7/21 (33)	N.S.
Overall		17/32 (53)	11/21 (52)	N.S.
> 50% of bladder involved: 1st course		10/33 (30)	9/20 (45)	N.S.
Overall		14/33 (42)	14/20 (70)	p.05
History of exophytic disease: 1st course		12/35 (34)	7/18 (39)	N.S.
Overall		20/35 (57)	8/18 (44)	N.S.
(b) Progression		Progression rates		
Risk factor		Present (%)	Absent (%)	
CIS-related bladder symptoms		11/32 (34)	5/21 (24)	N.S.
History of exophytic disease		12/35 (34)	4/18 (22)	N.S.
> 50% of bladder involved		13/33 (36)	3/20 (15)	P < 0.06
Failed to enter CR		10/21* (48)	3/29 (10)	P < 0.005

* 3 patients whose disease progressed during the first course of BCG were excluded from this analysis.

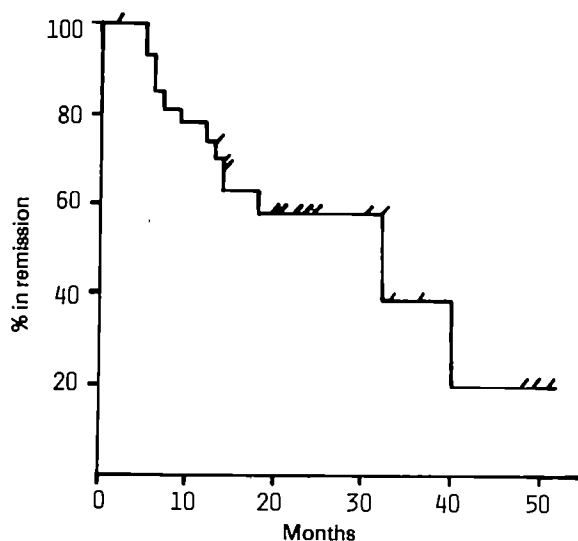


Fig. Duration of complete remission induced by BCG

Treatment-related side effects and response to treatment

Over half of the patients experienced minimal or no bladder symptoms during the first course of treatment (cumulative symptoms score 0–5). This did not preclude their responding to treatment, however (Table 3), and many of the patients with symptomatic CIS noticed a marked improvement in their symptoms during the first few treatments.

There was a trend towards a relationship between response to the first course and severity of symptoms but this did not reach statistical significance. No such trend was seen with the second course, where it was noted that several patients failed to respond despite experiencing severe bladder side effects. The severity of bladder symptoms was significantly greater during the second course ($P < 0.01$).

No treatment-related fever was experienced in these patients.

Day 7 urine white cell counts

The cell counts performed prior to each treatment tended to increase during a course but showed no tendency to be higher in responders than non-responders. Cell counts were significantly higher in the second course than the first ($P < 0.025$).

Treatment failure

Failure to respond to intravesical BCG manifested itself in a number of ways (Table 4).

- Disease progression occurred during the first course of treatment in 3 patients.
- In 4 patients the CIS cleared but papillary disease persisted. Three of these patients developed disease progression within 6 months of treatment. The other has retained his bladder and is well at 14 months.
- "True" failure occurred in 6 patients with persistent CIS on biopsy after 2 treatment courses. Two cystectomies were performed, the remaining patients being considered unsuitable because of their age or coexistent disease. Two of 4 patients have progressed but the others remain well at 17 and 34 months.
- Nine patients had persistently positive urine cytology despite negative bladder biopsies. The source of malignant cells has become apparent in 6 patients but not before progression had occurred in 5 of them, the origin being prostate (2 patients), bladder (2), lower ureter (2) and renal pelvis (1)—this last patient also having bladder disease.

Relapse of disease

Of patients entering CR 12 have relapsed (Table 5). Three were found to have progressed by the time the site of recurrent disease was found. Of the other 9, none has progressed, though only 3 are back in CR, patients receiving a variety of treatments. All patients had positive cytology at the time of

Table 3 Treatment-related Bladder Symptoms

Cumulative symptom score	Success rate	
	1st course (%)	2nd course (%)
0–5	8/29 (29)	4/8 (50)
6–10	6/13 (46)	1/4 (25)
> 11	5/11 (45)	4/9 (44)
Total	19/53	9/21
Mean symptom score ($\pm$ SE)	7 $\pm$ 1	16 $\pm$ 3

Table 4 Outcome in Treatment Failures

Mode of failure	No	Progressed
Progression during first course	3	3
Clearance of CIS, but persistent papillary disease	4	3
Persistent CIS on biopsy	6	2
Negative biopsies, positive cytology	9	5
Total	22	13

Table 5 Relapse following CR on BCG

Site of relapse	No.	Back in CR	Progressed
Bladder	8	2	2
Prostate	2	1	1
Ureters	1	0	0
Unknown	1	0	0
Total	12	3	3

histological relapse—in most cases it was found to have become positive several months beforehand.

Disease progression

Overall, 16 of the 53 patients (30%) have developed muscle-invasive disease. The presence of CIS-related bladder symptoms and a history of exophytic bladder disease were not predictive of disease progression (Table 2b). Failure to achieve CR was strongly associated with progression, whilst extent of CIS within the bladder was of borderline significance.

No relationship between CIS-related symptoms and extent of disease was found.

Discussion

The ability of intravesical BCG to induce complete remissions in CIS of bladder has again been demonstrated in this series. The proportion of patients entering CR at 53% is rather lower than the overall CR rate of 69% given in a review of series involving 300 patients (Reitsma *et al.*, 1989). The causes of this might relate to the patient population under treatment, the strain of BCG used and the dose used. The Evans strain has, however, been used in Edinburgh with a very good initial response rate in CIS of bladder (Cumming *et al.*, 1989), given in higher dosages—in fact the total dose of BCG given per course in this study (16 ampoules weekly $\times$ 6) is just over half of that given in Edinburgh (20 ampoules weekly $\times$ 8). This may account for the surprisingly low incidence of side

effects in this study. It is difficult, however, to find evidence to support the use of higher concentrations, for although there was a trend for patients who reported more severe bladder symptoms in the first course to have a higher response rate, the effect was small and not significant. Furthermore, urinary cell counts 7 days after each treatment, which might give a more objective measure of BCG-induced bladder inflammation (though subject to the confounding influence of variable urine formation rates), bore no relationship to response to treatment.

There is surprisingly little information on the duration of BCG-induced CR in CIS of bladder. Herr *et al.* (1986) reported a median remission duration of 5 years. The corresponding figure in this study (32 months) is only just over half of that. It is possible that the reduced treatment intensity in this study accounts for the difference, though remissions induced by a second course lasted no longer than those induced by the first despite the greater associated toxicity and inflammatory exudate. Our result is consistent with that of Brosman (1989), 40% of whose patients had relapsed by 24 months despite maintenance therapy for 1 year.

The most important message from this study is that CIS of bladder remains a very dangerous condition, despite modern treatment, with 30% of patients developing progressive disease with a median observation time of only 32 months. Identifying those most at risk is problematical. This study would seem to confirm an earlier observation (Riddle *et al.*, 1976) that extent of bladder involvement is an important determinant of disease progression. A more potent touchstone is response to intravesical BCG, the rate of progression being 5 times higher in the non-responders (48 vs 10%). Patients who have failed intravesical BCG should be considered for radical surgery.

This policy would probably be defensible even in those patients with negative bladder biopsies, but who persist in having malignant cells in the urine. In this series 9 patients were in this situation and 5 of them have progressed. A prophylactic cystourethrectomy would have saved all but one of these patients (who developed a simultaneous bladder and renal pelvis tumour). At the very least a search should be made for the source of the cells, performing an intravenous urogram, careful cystoscopic examination, selective ureteric urine cytology, random bladder biopsies and a transurethral resection biopsy of prostate.

Patients who enter remission are not free from danger and must be followed up closely. The relapse rate is high and in this series 25% of those who

relapsed had progressed by the time histological recurrence was found. All patients had positive cytology at relapse. It is probable that urine cytology is the single most important investigation in the follow-up of patients in CR (Highman *et al.*, 1988). It is possible that more assiduous cytological monitoring would allow the early application of treatments to forestall tumour progression. Where superficial relapse of disease is diagnosed the patient may well be amenable to further conservative treatment. None of the 9 patients with superficial recurrence has progressed, though only 3 of them are back in CR. Further follow-up will be required to ascertain the safety of this policy.

Acknowledgements

The authors thank Sister E. Fenwick for clinical assistance and Mrs G. Thomson for typing the manuscript.

References

- Brosman, S. (1989). The influence of Tice strain BCG treatment in patients with transitional cell carcinoma *in situ*. In *Progress in Clinical and Biological Research, Volume 30; EORTC Genitourinary Group Monograph 6 BCG in Superficial Bladder Cancer*, ed. Debruyne, F. M. J., Denis, L. and van der Meijden, A. P. M. Pp. 193–206. New York: Liss.
- Cumming, J. A., Hargreave, T. B., Webb, J. N. *et al.* (1989). Intravesical Evans Bacille Calmette-Guérin in the treatment of carcinoma *in situ*. *Br. J. Urol.*, **63**, 259–263.
- Herr, H. W., Pinsky, C. M., Whitmore, W. F. *et al.* (1986). Long-term effect of intravesical bacillus Calmette-Guérin on flat carcinoma *in situ* of the bladder. *J. Urol.*, **135**, 265–267.
- Highman, W. J. (1988). Flat *in situ* carcinoma of the bladder: cytological examination of urine in diagnosis, follow-up, and assessment of response to chemotherapy. *J. Clin. Pathol.*, **41**, 540–546.
- Reitsma, D. J., Gulman, P., Lamm, D. L. *et al.* (1989). Long-term effect of intravesical bacillus Calmette-Guérin (BCG) Tice strain on flat carcinoma *in situ* of the bladder. In *Progress in Clinical and Biological Research, Volume 30 EORTC Genitourinary Group Monograph 6 BCG in Superficial Bladder Cancer*, ed. Debruyne, F. M. J., Denis, L. and van der Meijden, A. P. M. Pp. 171–186. New York: Liss.
- Riddle, P. R., Chisholm, G. D., Trott, P. A. *et al.* (1976). Flat carcinoma *in situ* of bladder. *Br. J. Urol.*, **47**, 829–833.

The Authors

- S. J. Harland, MD, MSc, MRCP, Senior Lecturer in Medical Oncology
- C. R. Charig, FRCS(Urol), formerly Research Registrar. Now Consultant Urological Surgeon, Epsom District Hospital.
- W. J. Highman, FRCPath, FIAC, Consultant Cytopathologist
- M. C. Parkinson, BSc, MD, FRCPath, Consultant Histopathologist
- P. R. Riddle, MS, FRCS, Consultant Urological Surgeon.

Requests for reprints to: S. J. Harland, Institute of Urology and Nephrology, Middlesex Hospital, Mortimer Street, London W1N 8AA.

Laparoscopic Pelvic Lymph Node Dissection

W. G. BOWSER, A. CLARKE, D. G. CLARKE and A. J. COSTELLO

Department of Urology, St Vincent's Hospital, Melbourne, Australia

Summary—The infiltration of pelvic lymph nodes by carcinoma of the prostate or carcinoma of the bladder is an important factor in disease staging. Until now, this could be accurately assessed only by means of open surgery, an undesirable option as an investigation. Recent advances in laparoscopic instruments and camera systems have allowed the performance of laparoscopic pelvic lymph node dissection. A series of dissections in 14 patients is reported.

There has been increasing interest recently in laparoscopic surgery, 90 years since Kelling (1902) presented his concept of “coeloscopy” at the Congress of German Naturalists and Physicians in Hamburg. The diagnostic potential of the technique was emphasised by Jacobaeus (1910), who also coined the word “laparoscopy”. Kalk (1929) developed new lens systems and is regarded as the father of modern laparoscopy. In 1989, Dubois *et al.* performed the first laparoscopic cholecystectomy, which spawned interest in the applications of laparoscopy to technically challenging surgical problems such as pelvic lymph node dissection.

Patients and Methods

A series of 12 patients had carcinoma of the prostate. Their disease was staged locally using rectal examination, transrectal ultrasonography and cystourethroscopy. All patients had histological evidence of carcinoma of the prostate following either transurethral resection ($n=4$) or ultrasound-guided needle biopsy using the “Biopty” gun ($n=8$). Screening for metastatic disease included serum acid phosphatase, serum prostate specific antigen (P.S.A. Hybritech radio-immunoassay), chest X-ray and radio-isotope bone scanning. Two patients had GIII pT2 carcinoma of the bladder. Both were originally diagnosed and staged using intravenous urography, cystoscopy, examination under anaesthesia, transurethral resection, chest X-ray and

pelvic and abdominal computed tomography (CT) scanning. One of these patients, a female, had been subjected to 4 courses of M-VAC chemotherapy after a laparotomy 8 months previously had revealed iliac nodes infiltrated by transitional cell carcinoma. Subsequent CT scanning had shown no evidence of residual lymphadenopathy. The other patient, a male, was subjected to laparoscopic node dissection to establish his suitability for radical cystectomy. Details of the patients are summarised in Tables 1 and 2.

Patients were admitted the day before surgery. Informed consent was obtained for both laparoscopic pelvic node dissection and laparotomy. Two units of blood were cross-matched. An enema was given on the night prior to surgery and an abdominal shave was performed. Antibiotic prophylaxis was not given routinely. All patients were prescribed T.E.D. anti-thrombotic stockings.

Under general anaesthesia, the patient was placed in the lithotomy position on Lloyd Davies stirrups with each arm beside the trunk. The pelvis was hyper-extended by placing a rolled blanket under the buttocks and the table given 10° of Trendelenburg tilt. The abdomen was prepared and draped to allow access to both iliac fossae. The surgeon stood on the side undergoing surgery, the camera operator opposite and the assistant between the patient's legs. A 14 F urethral catheter was placed in the bladder and left on free drainage. A Veress needle was inserted through a sub-umbilical incision and a pneumoperitoneum produced and maintained at 14 mm Hg. An 11 mm trocar was inserted through this incision and the telescope

Table 1 Carcinoma of the Prostate

<i>Patient no.</i>	<i>Age (years)</i>	<i>P.S.A (µg/L)</i>	<i>Previous abdominal surgery</i>	<i>Pre-operative staging (TNM)</i>	<i>Gleason grade (primary tumour)</i>	<i>Node histology</i>
1	70	43.4	No	T3NXMO	6	Negative
2	69	16.5	No	T2bNXMO	5	Negative
3	64	142.0	No	T3NXMO	7	Positive
4	71	6.0	Yes	T1bNXMO	6	Negative
5	76	90.0	No	T3NXMO	8	Negative
6	76	8.3	No	T3NXMO	2	Negative
7	65	26.4	Yes	T2aNXMO	5	Negative
8	69	68.0	No	T3NXMO	8	Negative
9	67	34.8	No	T3NXMO	8	Positive
10	73	55.0	Yes	T3NXMO	6	Negative
11	60	42.0	No	T3NXMO	8	Negative
12	73	11.8	No	T2bNXMO	5	Negative

Table 2 Carcinoma of the Bladder

<i>Patient no.</i>	<i>Age (years)</i>	<i>Previous abdominal surgery</i>	<i>Pre-operative staging (TNM)</i>	<i>Node histology</i>
13	72	Yes	pT2NXMO	Negative
14	68	Yes	pT2NXMO	Negative

inserted into the peritoneal cavity to visualise the crucial landmarks on the television monitors. Where necessary, the Trendelenburg tilt was increased to displace bowel from the pelvis.

Two 10 mm ports were placed in the right iliac fossa under camera vision and used with 5 mm adaptors as working channels. Blunt grasping forceps were used to pick up the peritoneum midway between the medial umbilical ligament and the pulsation of the external iliac artery. A peritoneal incision was then made between these 2 structures using hook diathermy and the peritoneal window extended using blunt dissection with 2 pairs of grasping forceps. The vas deferens was identified at the base of the wound, lifted with the hook diathermy, coagulated and divided. The medial aspect of the external iliac vein was then exposed by teasing the adjacent fat with 2 pairs of blunt grasping forceps. The lymph nodes in the area between the medial aspect of the external iliac vein, the pelvic side wall and over the obturator nerve were then cleared using blunt grasping forceps, hook diathermy and diathermy scissors. Nodes were removed piecemeal through the most convenient 10 mm port after removing the 5 mm adaptor or, when necessary, the endoscope was moved to 1 of the 10 mm ports and the nodes

extracted through the 11 mm port in 11 mm cup forceps. Bleeding small vessels were secured using either coagulating diathermy or clips after they were clearly seen with the help of a suction irrigation device (irrigating with 1000 units heparin/L of Hartmann's solution). The 10 mm ports were then removed and the associated wounds closed with nylon.

The procedure was then repeated on the left, retracting the sigmoid colon, where necessary, in blunt grasping forceps. At the end of each operation, haemostasis was carefully checked using irrigation and aspiration of the operative fields. After desufflation of the abdomen, wounds were closed with nylon. All nodes were sent for paraffin section.

When the nodes appeared to be infiltrated by carcinoma, an individual node biopsy was performed: a node was dissected free using blunt dissection with grasping forceps and sharp dissection with diathermy scissors, removed in 11 mm cup forceps through the 11 mm port and sent for frozen section. When this proved positive, the dissection went no further.

If persistent bleeding could not be controlled during the operation, a laparotomy was performed, haemostasis obtained and the operation completed by open operation.

Results

No patient had evidence of distant metastases. The mean operation time was 1 h 50 min (range 45 min–3 h). Five patients had unilateral dissections and 6 had bilateral dissections. A mean number of 5

lymph nodes was dissected per side. Two patients with carcinoma of the prostate had positive nodes: in 1 of these, this was confirmed by frozen section. Both patients with carcinoma of the bladder had negative nodes.

In 3 patients the operation was completed by necessity as an open procedure; 2 of these patients had persistent bleeding from a branch of the obturator artery and 1 bled from the inferior epigastric artery near its origin. Only 1 patient required a blood transfusion (2 units).

All patients had an uneventful post-operative recovery. Following laparoscopic dissection, all were discharged the morning after surgery.

Discussion

Lymph node dissection is the most accurate method available for assessing pelvic lymph node involvement with carcinoma of the prostate. Both computed tomography and nuclear magnetic resonance imaging are unlikely to detect tumour in normal-sized nodes (Chadwick *et al.*, 1991). Pedal lymphography is less accurate than node dissection (O'Donoghue *et al.*, 1976) and prostatic lymphoscintigraphy lacks the precision and clarity required for disease staging (Stone *et al.*, 1979).

Careful histological examination of pelvic lymph nodes may avoid inappropriate local therapy for carcinoma of the prostate (McDowell *et al.*, 1990). There is evidence that once this disease has spread to pelvic nodes, distant metastases can be expected within 2 to 3 years (Catalona and Kelly, 1983). Knowledge of such nodal disease may be sufficient evidence to institute early hormonal therapy (Pollan, 1983; van Aubel *et al.*, 1985).

In the past, pelvic node dissection for carcinoma of the prostate has been criticised owing to the risk of lymphocele, suprapubic and genital oedema and thromboembolic disease. The technique for laparoscopic node dissection includes some modifications which are important in this respect. The incidence of lymphoedema is greatly reduced by leaving the deep inguinal nodes and those along the lateral border of the external iliac artery, and the risk of venous thrombosis is reduced by avoiding manipulation of the pelvic veins (Lytton, 1986). Furthermore, the incidence of lymphocele is likely to be reduced by a transperitoneal approach.

The general techniques for laparoscopic abdominal surgery have been described elsewhere (Semm and Friedrich, 1987). There are 3 specific points which are critical in the performance of laparo-

scopic pelvic lymph node dissection. Firstly, it is worthwhile spending some time examining the anatomical landmarks to ensure the correct positioning of the peritoneal window over the pelvic nodes. If this window is incorrectly positioned, even by millimetres, the potentially straightforward dissection on to the vas and pelvic nodes will prove difficult and time-consuming.

Secondly, it is important to examine the nodes carefully *in situ*. If there is reasonable suspicion that the nodes are positive, a single node biopsy by sharp dissection followed by frozen section is indicated. This ensures that the unnecessary dissection of positive nodes, with its inherent risk of bleeding, is avoided. The result of the patient's pre-operative prostatic specific antigen may give some guidance to the likelihood of nodal involvement.

Thirdly, as for all laparoscopic surgery, haemostasis should be even more meticulous than at open surgery. Quantifying blood loss is difficult laparoscopically and haemostasis should be checked and checked again using irrigation and aspiration. With experience, the use of diathermy and clips to stop bleeding, even from small vessels, becomes easier.

The operation can be considered for those who have undergone previous abdominal surgery, although careful precautions must be taken when introducing the Veress needle, insufflating the abdomen and introducing trocars (Semm and Friedrich, 1987). For thoroughness, a bilateral dissection is preferable. The unilateral dissections were performed early in the series. With increased operating speed, bilateral laparoscopic dissection has become routine.

The positioning of the surgeon and assistants, as with open surgery, is a matter of personal preference. Unlike Schuessler *et al.* (1991), we have not found that it is difficult, for example, to operate with laparoscopic instruments in the right pelvis whilst standing on the patient's right.

The use of laparoscopic pelvic node dissection has several implications. The surgical assault on the patient is lessened, resulting in a comfortable and speedy return to normal activity. The operation is possible without making great demands on hospital bed occupancy. As a result, node dissection is more appealing as an investigation and staging procedure. If nodal status is known, a fairer comparison of treatments is possible: for example, a more accurate audit of the results of radical prostatectomy versus radiotherapy for localised carcinoma of the prostate. It may also prove to be a useful technique in the staging and management of carcinoma of the bladder.

Acknowledgements

W.G.B. is grateful for the Shackman Travelling Fellowship and the Sir Alexander McCormick Travelling Fellowship of the Royal College of Surgeons of England. The authors are also indebted to Dr R. Stillwell of the Department of Pathology, St Vincent's Hospital, for his examination of the specimens

References

- Catalona, W. J. and Kelly, D. R. (1983). Accuracy of frozen section detection of lymph node metastases in prostatic carcinoma. *J. Urol.*, **127**, 460.
- Chadwick, D. J., Cobby, M., Goddard, P. *et al* (1991). Comparison of transrectal ultrasound and magnetic resonance imaging in the staging of prostate cancer. *Br. J. Urol.*, **67**, 616–621.
- Dubois, F., Bertelot, G. and Levard, H. (1989). Cholécysectomie par coelioscopie. *Presse Med.*, **118**, 980–982.
- Jacobaeus, H. C. (1910). Ueber die Möglichkeit die Zystoskopie bei Untersuchung seröser Höhlungen anzuwenden. *Muenchen. Med. Wchnschr.*, **57**, 2090–2092.
- Kalk, H. (1929). Erfahrungen mit der Laparoskopie (zugleich mit Beschreibung eines neuen Instrumentes). *Ztschr. Klin. Med.*, **111**, 303–348.
- Kelling, G. (1902). Ueber Oesophagoskopie, Gastroskopie und Kolioskopie. *Muenchen. Med. Wchnschr.*, **49**, 21–24.
- Lytton, B. (1986). Early prostatic cancer. In *The Prostate*, ed. Blandy, J. P. and Lytton, B. Chapter 12, p. 166. London: Butterworths.
- McDowell, G. C., Johnson, J. W., Teaney, D. *et al* (1990). Pelvic lymphadenectomy for staging clinically localized prostate cancer. *Urology*, **35**, 476–482.
- O'Donoghue, E. P. N., Shridhar, P., Sherwood, T. *et al*. (1976). Lymphography and pelvic lymphadenectomy in carcinoma of the prostate. *Br. J. Urol.*, **48**, 689–696.
- Pollen, J. J. (1983). Endocrine treatment for prostatic cancer. *Urology*, **21**, 555–558.
- Schuessler, W. W., Vancallie, H. R., Reich, H. *et al* (1991). Transperitoneal endosurgical lymphadenectomy in patients with localised prostate cancer. *J. Urol.*, **145**, 988–991.
- Semm, K. and Friedrich, E. R. (1987). *Operative Manual for Endoscopic Abdominal Surgery*. Chicago: Year Book Medical Publishers.
- Stone, A. R., Merrick, M. V. and Chisholm, C. D. (1979). Prostatic lymphoscintigraphy. *Br. J. Urol.*, **51**, 556–560.
- van Aubel, O. G. J. M., Hoekstra, W. J. and Schröder, F. H. (1985). Early orchiectomy for patients with stage D1 prostatic carcinoma. *J. Urol.*, **134**, 292.

The Authors

W. G. Bowsher, MA, MChir, FRCSUrol, Lecturer in Urology, The Royal London Hospital. Now Senior Fellow in Urology, St Vincent's Hospital
 A. Clarke, MB,BS, Research Fellow, Department of Urology.
 D. G. Clarke, MB,BS, Research Fellow, Department of Urology.
 A. J. Costello, FRACS, Head of Department of Urology.

Requests for reprints to W. G. Bowsher, Department of Urology, St Vincent's Hospital, 41 Victoria Parade, Fitzroy, Victoria 3065, Australia.

Is Urethral Pressure Profilometry Useful in the Pre-operative Assessment of Benign Prostatic Hyperplasia?

C. R. CHAPPLE, S. W. COPPINGER and R. T. TURNER-WARWICK

Department of Urology, Middlesex Hospital, London

Summary—The principal aim of this study was to provide an objective assessment of the potential role of urethral pressure profilometry as a technique for assessing prostatic size by direct comparison with endoscopic assessment of prostatic length and computed tomographic measurement of prostatic volume and length. There was a poor correlation between pre-operative prostatic length and amount resected in the operating theatre. The results obtained with urethral pressure profilometry correlated poorly with those obtained using the other techniques, and cannot therefore be relied upon in routine clinical practice. Although there was good correlation between the length of the prostate and prostatic size, assessed by pre-operative computed tomography, this correlated poorly with the amount of tissue resected at operation. Further studies need to be conducted to compare objectively the completeness of prostatic resection with the outcome following prostatectomy.

Clinical assessment of the prostate is an essential part of the evaluation of the patient presenting with symptoms of benign prostatic hyperplasia. Although little correlation has been shown between the size of the gland and the degree of outflow tract obstruction (Turner-Warwick *et al.* 1973), it is well recognised that per-operative complications, including blood loss and irrigant absorption, are related to the amount of tissue resected endoscopically. Therefore, any technique which could provide an accurate pre-operative evaluation of the amount of obstructing prostatic tissue present would be of value in planning surgery.

Urethral pressure profilometry (UPP) has been advocated for use in the urodynamic evaluation of patients to provide detailed information on prostatic length and intraprostatic urethral pressure. It is inexpensive and quick to perform when used in conjunction with existing urodynamic equipment and has been reported to be of value in the diagnosis of bladder outlet obstruction in the male patient (Abrams, 1976).

Surprisingly, there have been no studies compar-

ing the actual urethral length measured during endoscopy or on detailed radiological investigation with the functional prostatic length obtained from UPP. The principal aim of this study was to provide an objective assessment of the potential value of UPP, by comparing the results for functional profile length and maximum intra-urethral closure pressure with urethral length measured endoscopically, and with prostatic size and length measured on computed tomography (CT) scanning. In addition, the relationship between prostatic size and the amount of adenoma resected at operation was examined.

Patients and Methods

A total of 21 patients were investigated with full informed consent. All patients underwent comprehensive urodynamic assessment using videocystometry (Bates *et al.*, 1970). CT scanning of the pelvis was performed using a Siemens Somatom D, which has an integrated package for measurement of volumes. Using this system, the prostatic outline was delineated and the prostatic length and volume calculated for each patient. The CT prostatic size

was expressed in arbitrary units and the interpretation of all scans was reviewed by a single consultant radiologist.

Urethral pressure profilometry was performed in 18 patients using the standard fluid filled technique described by Brown and Wickham (1969), and taking account of the observations of Abrams *et al.* (1978). An Ormed 5000 machine was used in conjunction with twin luminal catheters, 1 lumen opening at the end of the catheter and the other at a point 5 cm proximal. Fluid perfusion was carried out at a rate of 10 ml/min and the catheter was withdrawn on a mechanical traction unit at a rate of 2 mm/s. The definitions used were those suggested by the International Continence Society (Abrams *et al.*, 1988). The measurements are represented diagrammatically in Fig. 1. The functional profile length was also calculated using the modification proposed as being more accurate by Kitada and Ishisawa (1981), namely: "the length from the most proximal pressure increase above bladder pressure to the position where the urethral pressure exceeds prostatic peak pressure". The

functional profile length was documented, as was the maximum urethral closure pressure at the bladder neck, within the prostate and at the distal sphincter mechanism.

Intraprostatic length was measured at endoscopy in 20 patients, before transurethral resection of the prostate (TURP), by placing the tip of the resectoscope at the bladder neck, marking the relative position of the instrument at the external meatus, and withdrawing it until the distal sphincter mechanism came into view. The difference between the 2 points on the shaft of the cystoscope was then carefully measured, the procedure repeated 3 times to ensure reproducibility, and the mean value recorded. The results of the CT scan and profilometry were not known to the endoscopist at the time of surgery. All prostatic chippings were weighed at the end of the procedure, in order to minimise errors in the weight due to subsequent desiccation within formol-saline.

The data were analysed using the SPSS^{*} statistical package, version 2.1, on an Amdal mainframe computer.

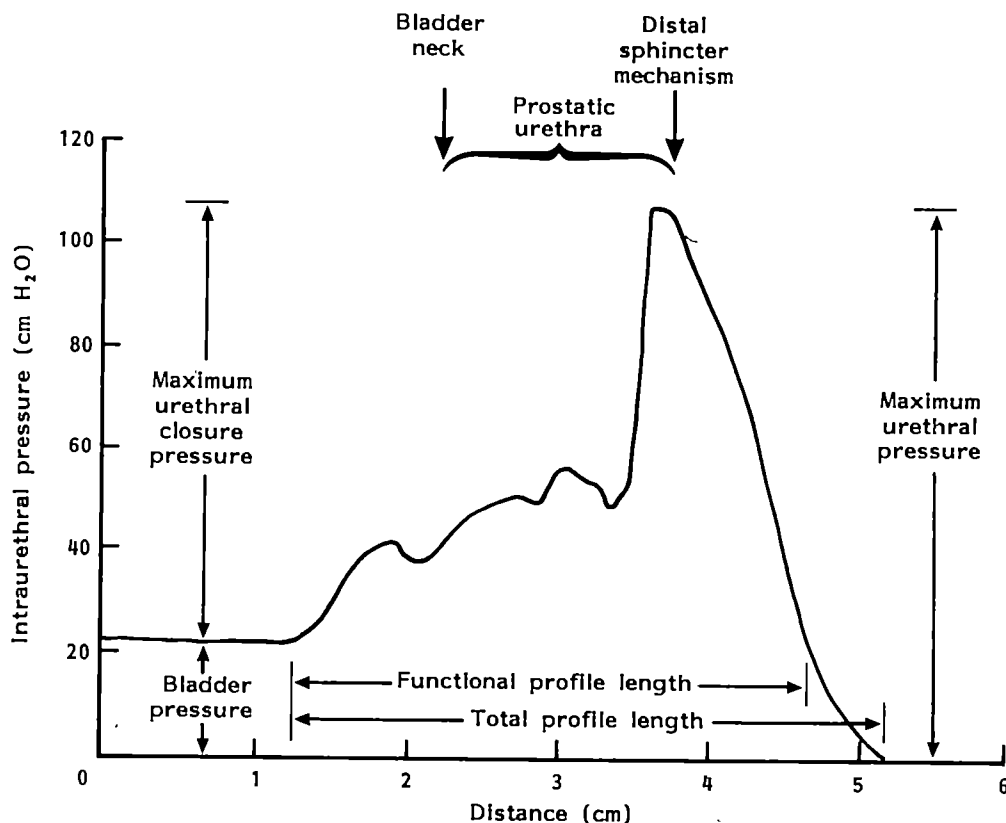


Fig. 1 Diagrammatic representation of the urethral pressure profile defining the terminology used in this study.

Results

The mean age of the patients was 68 ± 1.45 years (range 57–80). The mean difference between the functional prostatic profile length and the CT prostatic length was 1.3 ± 0.25 cm (95% C.I. 0.81 to 1.79). The mean difference between the functional prostatic profile length and the measured endoscopic length was 1.77 ± 0.24 cm (95% C.I. 1.30 to 2.23). In comparison, the mean difference between the CT length and the endoscopic length was only -0.46 ± 0.11 cm (95% C.I. -0.26 to -0.67).

Comparison of direct endoscopic measurement with CT derived urethral length showed a highly significant correlation (Fig. 2). While there was a statistically significant correlation between CT length and functional profile length, Fig. 3 shows that the line of best fit does not intersect at the zero co-ordinates and is shifted up the y axis, suggesting that UPP tends to overestimate urethral length. Plotting endoscopic length against functional profile length (Fig. 4) shows the same relationship. Using the correction proposed by Kitada and Ishisawa (1981), the mean value for functional profile length decreased from 5.71 ± 0.218 to 5.36 ± 0.206 cm, but the correlation of this 'new' value with endoscopic urethral length remained poor at $r = 0.700$.

There was good correlation between the length of the prostate and prostatic size, assessed by computed tomography (Fig. 5). However, comparison of the maximum urethral closure pressure and CT prostatic size showed no association (Fig. 6). There was a poor correlation between the size of

the prostate before surgery as measured by CT scan and the amount of tissue resected at operation (Fig. 7).

Discussion

Direct measurement of urethral length at endoscopy appears to provide an accurate and reproducible assessment of urethral length. The surgical landmarks are easily visualised and we found it possible consistently to measure the urethral length in a reproducible manner.

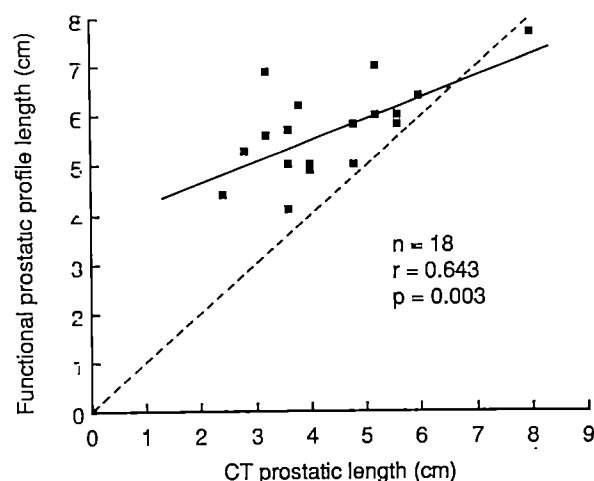


Fig. 3 CT prostatic length as contrasted to the functional prostatic profile length demonstrating the tendency for urethral pressure profilometry to overestimate prostatic length.

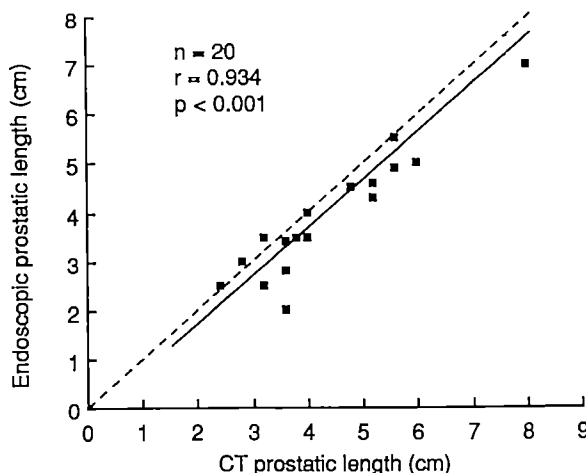


Fig. 2 Comparison of the prostatic length measured endoscopically (y axis) and by computed tomography (x axis). There is a close correlation between these measurements $r = 0.934$.

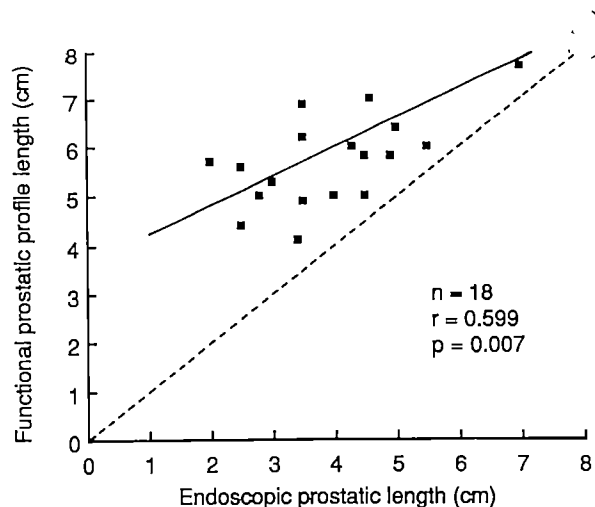


Fig. 4 Endoscopic prostatic length contrasted to the functional prostatic profile length demonstrating the tendency for urethral pressure profilometry to overestimate prostatic length.

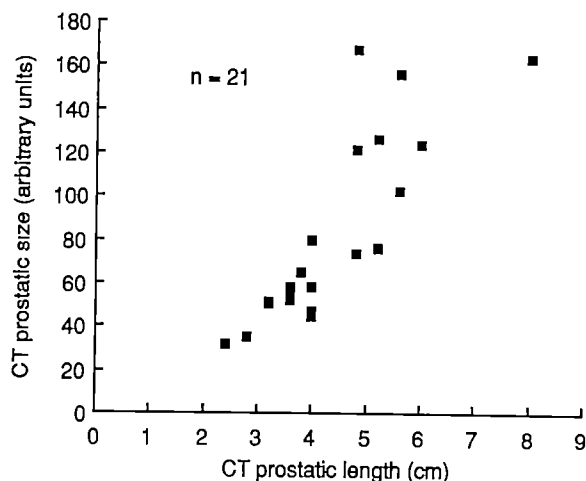


Fig. 5 Prostatic length and size as assessed by CT scanning are well correlated.

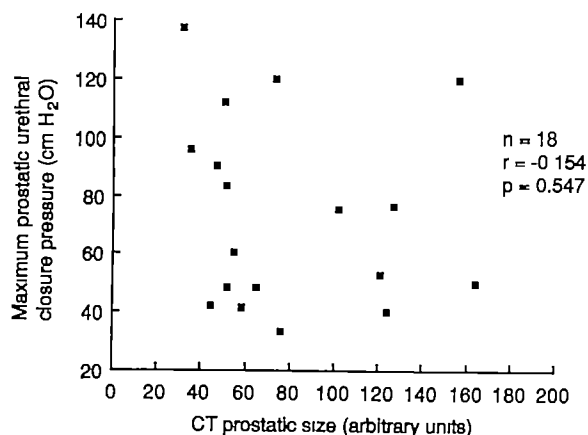


Fig. 6 The maximum prostatic urethral closure pressure is poorly correlated with the prostatic size as assessed by CT scanning.

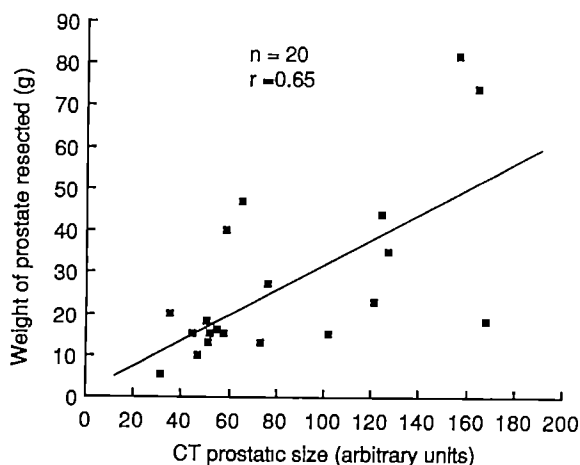


Fig. 7 There is a limited correlation between the prostatic size assessed on CT scanning and the amount which is resected.

Computed tomography of the prostate was used to provide a comparator of UPP and endoscopic measurement. Transrectal ultrasound does not involve radiation and can be used to measure prostatic size, but it does not provide a measurement of length analogous to direct measurement or profilometry, as the distal sphincter mechanism cannot be localised unequivocally. In contrast, the distal sphincter mechanism can be readily delineated on CT scanning by reference to adjacent structures within the perineum, including the perineal membrane. The excellent agreement between direct and CT measurement of length, and the correlation between prostatic length and size using CT scanning, validate its use as a research technique.

The reproducibility and close relationship between endoscopic and CT derived urethral length and the clear association between CT prostatic size and CT prostatic length with a correlation coefficient $r=0.829$ (Fig. 5) suggest that estimation of prostatic length prior to resection serves as a simple and accurate guide to prostatic size. Despite this we found a poor correlation ($r=0.65$, Fig. 7) between the estimated pre-operative prostatic size and the amount resected at surgery. With the advent of accurate and relatively non-invasive methods of estimating the initial size of the prostate it is important to examine critically the relationship between the extent of resection and long-term outcome; this should be helpful in resolving the debate as to what constitutes an adequate prostatic resection.

We found no association between the maximum intraprostatic urethral closure pressure and the size of prostate. This latter finding supports the clinical axiom that prostatic size does not necessarily correlate with the degree of outflow tract obstruction. This poor correlation may partly reflect fluctuations in the neurally mediated "dynamic" component of outflow obstruction (Furuya *et al.*, 1982). As the circumstances attending urodynamic investigation are not usually conducive to a relaxed state, the variable neural stimulation engendered would be expected to lead to wide variations in intraprostatic pressure.

The functional prostatic profile length did show some statistical correlation with the CT length (Fig. 3), as did the endoscopic length (Fig. 4), but this relationship was skewed so that profilometry consistently overestimated the length of the intraprostatic urethra. Kitada and Ishisawa (1981) measured the urethral length using UPP and found a correlation between it and the length of the largest

lateral lobe following open prostatectomy. In order to obtain a significant correlation they re-defined the urethral length. Despite making allowance for this correction in this study, the correlation coefficient between functional profile length and endoscopic length was still poor ($r=0.700$).

The most likely explanation for the tendency of the UPP to overestimate the prostatic length is that the prostate gland extends beyond the "distal" sphincter active zone. Support for this suggestion is provided by the observations of Shah *et al.* (1979), who reported that the proportion of prostatic tissue distal to the verumontanum varies between 10 and 50%, with a value of up to 20% in 58% of patients. These findings explain both the excellent correlation noted previously between functional profile length and length of adenoma resected at open surgery (Kitada and Ishisawa, 1981) and the tendency evident in our study for urethral profilometry to overestimate "resectable" prostatic urethral length.

References

- Abrams, P., Blaivas, J. G., Stanton, S. L. *et al.* (1988). The International Continence Society. The standardisation of terminology of lower urinary tract functions *Scand. J. Urol. Nephrol.*, Suppl. 114, 5-19.
- Abrams, P. H. (1976). Sphincterometry in the diagnosis of male bladder outflow obstruction. *J. Urol.*, **116**, 489-492.
- Bates, C. P., Whiteside, C. G. and Turner-Warwick, R. T. (1970). Synchronous cine/pressure/flow/cysto-urethrography with special reference to stress and urge incontinence. *J. Urol.*, **42**, 714-733.
- Brown, M. and Wickham, J. E. A. (1969). The urethral pressure profile. *J. Urol.*, **41**, 211-217.
- Faruya, S., Kumamoto, Y., Yokoyama, Y. *et al.* (1982). Alpha-adrenergic activity and urethral pressure in prostatic zone in benign prostatic hypertrophy. *J. Urol.*, **128**, 836-839.
- Kitada, S. and Ishisawa, N. (1981). Urethral pressure profilometry in the pre-operative assessment for prostatectomy. *J. Urol.*, **126**, 89-91.
- Shah, P. J. R., Abrams, P. H., Feneley, R. C. L. *et al.* (1979). The influence of prostatic anatomy on the differing results of prostatectomy according to the surgical approach. *Br. J. Urol.*, **51**, 549-551.
- Turner-Warwick, R. T., Whiteside, C. G. and Arnold, E. P. (1973). A urodynamic view of prostatic obstruction. *J. Urol.*, **45**, 631-645.

The Authors

C. R. Chapple, MD, FRCS, Senior Urological Registrar.
S. W. Copping, FRCS, Urological Research Fellow.
R. T. Turner-Warwick, DSc, FRCS, FACS, FRACS, Consultant Urologist.

Requests for reprints to: C. R. Chapple, Department of Urology, The Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF.

A 12-Week Placebo-controlled Double-blind Study of Prazosin in the Treatment of Prostatic Obstruction due to Benign Prostatic Hyperplasia

C. R. CHAPPLE, M. STOTT, P. H. ABRAMS, T. J. CHRISTMAS and E. J. G. MILROY

Department of Urology, Middlesex Hospital, London; Department of Urology, Ham Green Hospital, Bristol

Summary—A series of 93 normotensive patients with benign prostatic hyperplasia and maximum urinary flow rates < 15 ml/s, treated at 2 hospital centres using an identical protocol, was randomly assigned to receive a 12-week course of treatment with prazosin or placebo in a double-blind parallel group trial. A total of 75 patients completed the study and were suitable for the final analysis. Prazosin was administered orally in doses of 0.5 mg and then 1 mg twice daily for 4 days and 2 mg twice daily for the remainder of the trial.

Patients on treatment with prazosin exhibited a significantly increased maximum urinary flow rate as compared with placebo, with a significant reduction in maximum voiding detrusor pressure. Prazosin therapy did not produce a significant effect on either frequency or standard parameters of detrusor instability. A double-blind overall assessment of drug efficacy and tolerance significantly favoured prazosin therapy. A total of 30 patients receiving prazosin and 28 receiving placebo reported varied adverse effects. Eighteen patients were excluded from the final analysis, 10 being withdrawn because of adverse effects, 7 on treatment with prazosin and 3 in the placebo group.

In long-term usage oral prazosin was well tolerated and appeared to improve obstructed voiding in patients with benign prostatic hyperplasia.

Benign prostatic hyperplasia is characterised by a clinical picture which is of insidious onset, produces variable symptoms and which, although fluctuating in severity, usually remains static for many years (Ball *et al.*, 1981). Although the symptom complex in benign prostatic hyperplasia results from urethral obstruction, many patients are more troubled by the “irritative” symptoms, the incidence of which is found to be strongly associated with the secondary detrusor instability which occurs in up to 75% of patients (Abrams, 1985).

The initial clinical application of adrenergic blockade to the lower urinary tract used the combined α_1 and α_2 adrenergic antagonist phenoxybenzamine and produced encouraging improvements in urinary flow and clinical symptoms in most clinical studies (Caine *et al.*, 1976; Boreham *et al.*, 1977; Caine *et al.*, 1978; Gerstenberg *et al.*,

1980; Abrams *et al.*, 1981; Abrams *et al.*, 1982), with few exceptions (Brooks *et al.*, 1983). The incidence of side effects in 30% of patients on treatment with phenoxybenzamine (Caine *et al.*, 1978) has, despite its clearly documented efficacy, precluded its more widespread acceptance in the treatment of benign prostatic obstruction. These adverse effects have been attributed to the blockade of pre-synaptic α_2 adrenoceptors which is thought to interfere with the normal negative feedback control of noradrenaline release at the pre-synaptic adrenergic nerve terminal, resulting in high circulating noradrenaline levels. The incidental observation that urinary incontinence developed in women during antihypertensive therapy with prazosin (Straughan 1978, Thien *et al.*, 1978) contributed to the recognition of the potential role of selective α_1 adrenoceptor blockade as therapy in the lower urinary tract. Following the initial work of Caine *et al.* (1976), pharmacological and ligand-

binding studies by a number of workers have demonstrated the functional and ultrastructural pre-eminence of $\alpha 1$ and $\alpha 2$ receptors within the stromal compartment of the prostate (Chapple *et al.*, 1989), thereby providing a scientific basis for the use of specific $\alpha 1$ blockade in the non-surgical management of benign prostatic hyperplasia.

Criticism has been levelled at the current literature which reports the efficacy of selective $\alpha 1$ blockade, since it is based on detailed study of short treatment periods (Wein, 1989), with little effect on urodynamic parameters other than the urinary flow rate. Certainly it must be borne in mind that the symptomatic consequences of secondary detrusor instability are the commonest cause of referral to the urologist and it is possible that longer periods of treatment are required to demonstrate a therapeutic effect. In order to address these questions we have investigated the safety and efficacy of prazosin in a 3-month double-blind parallel placebo-controlled study, carried out in 2 centres using an identical protocol.

Patients and Methods

Patients

Candidates for the trial were 93 normotensive males with severely symptomatic benign prostatic hyperplasia who were on a waiting list for prostatectomy. Informed consent was received from all participants. All patients had a free urinary flow rate < 15 ml/s over a voided volume preferably in excess of 150 ml and were confirmed to have bladder outflow obstruction at the prostatic level using videocystometry. Patients with other conditions giving rise to urinary symptoms and reduced flow rate were excluded; urine bacteriology and cytology and, where necessary, a flexible cystoscopy were carried out. Other reasons for exclusion were: previous prostatic surgery, serum creatinine > 200 mmol/l, hypertension, poorly controlled diabetes, a history of myocardial infarction or stroke within the preceding 6 months, orthostatic hypertension and the presence of heart failure. Also excluded were patients taking medication that might affect bladder function, those on antihypertensive drug therapy and prior hypersensitivity to α adrenoceptor blocking drugs.

Study design

A double-blind, parallel-group protocol was followed at 2 centres (A—Ham Green Hospital, Bristol; B—Middlesex Hospital, London). After

baseline evaluation for 1 week, patients were randomly assigned to receive treatment with orally administered prazosin or placebo twice daily for 12 weeks. Prazosin or the placebo was administered in doses of 0.5 mg twice daily for 4 days, 1 mg twice daily for 4 days and 2 mg twice daily for the remainder of the trial. The randomised groups included 51 patients with concurrent disorders (26 receiving prazosin and 25 placebo) and 41 who received concurrent medication (20 prazosin and 21 placebo). A dose reduction facility existed for patients exhibiting adverse effects which could not be tolerated, allowing for them to continue in the trial on a lower dose (1 mg *bd*). Of the 75 patients included in the final assessment, 72 received the target daily dosage of 4 mg prazosin or the corresponding placebo. In 4 patients dose reduction was carried out, 3 of these patients being on prazosin and the fourth on placebo.

Assessment

Initial patient assessment included a medical history and physical examination, microscopy and culture of urine, blood urea and creatinine determination, radiographic examination of the chest and electrocardiogram. Heart rate and blood pressure were measured with the patient supine and standing. A detailed history of urinary symptoms was also obtained and these were scored using an arbitrary scale, to aid assessment of their severity. Upper tract pathology was excluded by the use of a routine X-ray examination of the abdomen and either a limited intravenous urogram or a renal ultrasound examination. If there were any doubts as to the clinical symptoms or suspicions of bladder pathology a flexible cystoscopy was carried out under local anaesthesia. Patients were instructed on the use of a diary card to document diurnal frequency of micturition; in addition, recording times of voiding and retiring allowed calculation of the frequency of micturition and nocturia. A baseline urodynamic assessment using videocystometry was obtained during the following week.

On a second visit, the adequacy of completion of diary cards was verified and those patients fulfilling entry criteria were started on the trial treatment. After 6 weeks of treatment, the patients returned to the hospital for a third visit when they were evaluated for completion of diary cards and for compliance with protocol and drug dosage. Patients were questioned about adverse events, and blood pressure and heart rate were measured.

On the final visit after 12 weeks of treatment,

compliance with treatment was checked by means of a capsule count, and adverse events were recorded from spontaneous reporting or from responses to specific questions. Urinary symptoms were evaluated and a second cystometric examination was performed. Patients were questioned as to their urinary flow and frequency of micturition. Investigators evaluated the overall efficacy and tolerance. Heart rate and blood pressure were measured after 5 min sitting and 2 min standing.

Cystometry

Patients presented at the clinic with a full bladder and voided into a flow meter immediately before undergoing videocystometry, thus providing a measurement of free maximum flow rate on micturition and the voided volume. The technique used for videocystometry was as previously described (Bates *et al.*, 1970). A filling catheter and a separate pressure line were passed into the bladder and a rectal pressure line was inserted. The volume of initial residual urine was estimated. All recorded values of detrusor pressure represented the result of subtraction of the rectal pressure from the total bladder pressure. The bladder was then filled to the maximum tolerated volume and the following filling variables were estimated: cystometric capacity, volume at the first unstable contraction, maximum pressure rise during filling and the end filling pressure. During voiding, after removal of the filling catheter, the cystometric (CMG) maximum flow rate, maximum and peak flow intravesical (detrusor) pressure on micturition were recorded. The end residual volume was calculated as the difference between the cystometric capacity and the volume voided. Urethral pressure profilometry was carried out at the end of each cystometrogram using the fluid fill technique described by Brown and Wickham (1969) (8F 2 side-hole catheter, perfused at 5 ml/min and withdrawn at 0.5 cm/s). All measurements conformed to the criteria and definitions specified by the International Continence Society (Abrams *et al.*, 1988).

Analysis of data and statistical methods

CMG data. The change between baseline and final assessments in continuous CMG variables was studied by 2-way analyses of variance, with treatment and centre as the 2 factors and fitting a linear model that included a hospital centre effect, a treatment effect and a centre by treatment interaction. Where the treatment by centre interaction was not significant at the 10% level this was dropped from the model. The results obtained for analysis

of variance were confirmed by an analysis of covariance (with the baseline value as covariate), which is more precise, and similar results were obtained.

Diary card data. Frequency of voiding per 24 h was calculated and nocturia was estimated from the number of voids falling between time to bed and time of rising. Since the time in bed differed from day to day and patient to patient this was converted to the equivalent rate per 8 h to allow for comparison. Mean values were calculated over the pre-treatment week and the final treatment week and were analysed using analysis for covariance as for the CMG variables. Changes from baseline in certain key variables were classified according to definitions of response supplied by the investigators. The proportion of patients responding in each treatment group were tabulated and the proportions in the 2 groups compared using Fisher's 2-tailed exact test.

Symptoms. A comparison of the distribution of baseline and final frequencies of symptoms in the 2 groups was carried out using log-linear modelling techniques. Centre effects were not evident and therefore the values were not fitted.

Subjective assessments. Patient's assessment of improved flow and reduced frequency, and physician's assessment of overall efficacy and toleration were each analysed using a 2-tailed Fisher's exact and chi-squared tests.

Results

Of the 93 patients entering the study, 10 withdrew because of side effects, 4 because of a concurrent illness and 4 for violations of the protocol. The remaining 34 patients in the prazosin group and the 41 in the placebo group were comparable in terms of age, weight, duration and character of symptoms, and renal function (Table 1). Therapy was administered to the prazosin group for an average of 87 days (range 79–104) and to the placebo group for an average of 86 days (range 79–107).

The results of the analysis of the urodynamic measurements of voiding efficiency are reviewed in Table 2. The mean free maximum flow rate increased significantly in the prazosin as compared with that of the placebo group ($P=0.01$) despite a significant reduction in the maximum micturition pressure whilst voiding in the prazosin as compared with the placebo group ($P=0.02$) (Fig.). The

Table 1 Demographic Data and Summary Statistics

Variable	Summary statistic	Treatment group	
		Prazosin	Placebo
Patients	No.	34	41
Age (years)	No. in range		
	<18	0	0
	18-45	1	0
	46-65	13	21
	>65	20	20
	Mean	66	64
	Range	40-85	52-76
Weight (kg)	Mean	75	76
	SD	13	11
	Range	57-117	54-109
Duration of symptoms (years)	Mean	3.2	3.1
Incidence of symptoms at baseline:			
urgency of micturition	No. of patients	22	22
hesitancy	No. of patients	12	18
poor stream	No. of patients	16	17
urge incontinence	No. of patients	20	26
frequency of micturition*	No. of patients	24	32
nocturia†	No. of patients	20	26
Blood urea	Mean	5.9	5.9
	Range	3.3-9.4	3.0-9.2
Creatinine	Mean	100	100
	Range	61-150	68-190

*Average of more than 7 voids per 24 h in baseline week.

†Average of at least 1 void per night in baseline week.

maximum detrusor pressure at peak urinary flow decreased but the change reached statistical significance in the data from centre B only. The changes observed in the other urodynamic parameters did not reach statistical significance.

No significant changes in the frequency of micturition or nocturia emerged from the voiding chart records for the 2 groups (Table 3) and questioning did not uncover any significant differences between the 2 groups for frequency of micturition, nocturia, urgency, urge incontinence, quality of urinary stream or hesitancy on micturition.

The investigators in the study evaluated the overall efficacy of the treatment at the end of the trial period on a scale of "excellent", "good", "none" and "poor" (Table 4). Some 56% of the ratings of the patients undergoing prazosin treatment were good or better, in contrast with only 21% for the comparable ratings of the placebo group ($P=0.02$, in favour of the prazosin treatment). A

similar rating of the toleration of active therapy was carried out during the study by the investigators (Table 5); risks were rated as "not significant" or "non-existent" for 68% of cases on active therapy as compared with 55% for placebo ($P=0.05$ in favour of prazosin). The results of this double-blind assessment of drug tolerance and efficacy is particularly surprising in view of the apparent absence of an improvement in diary card data or subjective assessment of urinary frequency.

An overall summary of adverse effects is presented in Table 6. Seven patients defaulted because of side effects in the active treatment group as contrasted to 3 with placebo; apart from an increased incidence of dizziness (16.7% versus 10%) and headache (12.6% versus 5%) on active versus placebo therapy respectively, the side effect profile was remarkably similar, with 30 patients developing side effects on prazosin and 28 on placebo. There was little apparent effect of active treatment as contrasted to placebo on sexual function. Mean

Table 2 Urodynamic Results from Both Centres

Variable	Baseline			Change from baseline			No. of patients					
	Centre	Prazosin (mean)	SD	Placebo (mean)	SD	Prazosin (mean)	95% CI	Placebo (mean)	95% CI	Prazosin	Placebo	P
Free maximum flow rate (ml/s)	A	11	3.6	9.7	3.2	-0.9	(-2.7, -1.0)	-3.4	(-5.3, -1.6)	14	14	0.01
	B	9	3.4	10	3.6	3.2	(1.5, 4.8)	0.6	(-0.9, 2.2)	20	23	
Initial voided volume (ml)	A	241.8	111.9	270	137.8	-87	(-142.9, -31)	-120.7	(-176.6, -64.7)	14	14	0.26
	B	144.2	76.2	160.7	73.4	32.8	(-16.9, 82.6)	-0.8	(-48, 46.4)	20	23	
Initial residual volume (ml)	A	79.8	73.6	109.5	72.2	-25.7	(-70.8, 19.4)	-49.7	(-92.8, -6.5)	11	13	0.29
	B	59.3	83.5	48.5	67.6	35.6	(-1.7, 72.8)	11.6	(-23.1, 46.3)	20	24	
CMG maximum flow rate (ml/s)	A	7.2	2.4	5.9	2.6	2.3	(-0.2, 4.8)	0.3	(-2.1, 2.6)	12	16	0.12
	B	10.9	6.2	10.8	5.3	6.1	(3.9, 8.2)	4.1	(2, 6.1)	20	24	
Final CMG volume (ml)	A	240.3	122.5	265.5	121.6	76.6	(-5.9, 159)	-24.4	(-95.9, 47)	12	16	0.35
	B	425	182.9	408	69.6	2.5	(-43.4, 48.3)	14.9	(-27, 56.8)	20	24	
Maximum voiding pressure (cm H ₂ O)	A	98	36	83	36	-14.2	(-26.9, -1.9)	0.8	(-10.8, 12.3)	12	16	0.02
	B	85.6	33.5	91.7	22.2	-17.1	(-27.7, -6.4)	-1.9	(-12, 8.2)	20	23	
End residual volume (ml)	A	35.5	81.7	46.5	69.2	6	(-28.2, 40.2)	16	(-15.6, 47.5)	12	16	0.56
	B	82.8	88.2	72.7	110.9	-1.1	(-30.3, 28.1)	8.9	(-18.4, 36.1)	20	24	

 Statistical significance: $P < 0.05$.

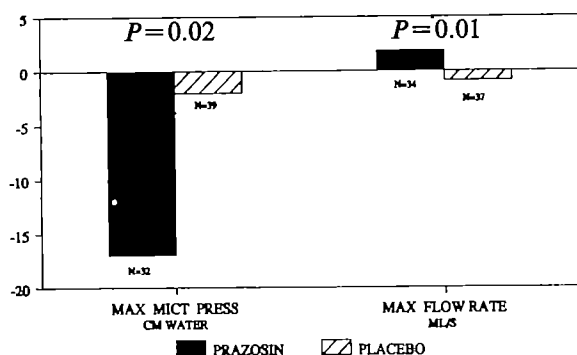


Fig. Mean change from baseline in voiding parameters, maximum micturition pressure (cm H₂O) and maximum flow rate (ml/s) on placebo therapy compared with prazosin. The discrepancy in the numbers of patients (total no. = 71, although 75 completed the study) is attributed to missing results in a few individuals due to technical errors.

fluctuations in supine and standing blood pressure and heart rate were minor and clinically insignificant; in particular, using a graduated increase in the therapeutic dose, no patients experienced the idiosyncratic first dose phenomenon which has been previously reported with prazosin when used as an antihypertensive agent. A total of 4 patients developed side effects necessitating dose reduction: 3 on active therapy and 1 in the placebo group.

Discussion

Total neural blockage using spinal anaesthesia produces a 47% reduction in urethral closure pressure (Furuya *et al.*, 1982) and α blockade similarly results in a decrease in urethral closure

pressure (Donker *et al.*, 1972). Dynamic changes such as these have in recent years highlighted the potential clinical importance of pharmacological blockade of the motor sympathetic adrenergic nerve supply to the prostate. Benign prostatic enlargement of the prostate comprises both hypertrophy and in particular hyperplasia of prostatic stromal and glandular compartments. Indeed, contrary to popular belief, morphometric quantitation of this tissue has suggested that hyperplasia of the stromal compartment is the predominant feature (Bartsch *et al.*, 1979). Although these authors did not carry out a separate analysis of the smooth muscle, it is likely that this would demonstrate a relative increase in the muscular component as contrasted to normal prostate. *In vitro* pharmacological studies have shown that the principal motor control of the prostate is via an action on α 1 adrenoceptors, which are localised predominantly within the stromal compartment of the prostate (Chapple *et al.*, 1989; James *et al.*, 1989).

Prazosin was introduced as an antihypertensive agent in 1977 (Cambridge *et al.*, 1977) and was subsequently reported to produce urinary incontinence (Straughan, 1978; Thien *et al.*, 1978). Subsequent *in vitro* muscle strip studies have demonstrated that prazosin produces effective α receptor blockade in the human prostate (Caine, 1986; Chapple *et al.*, 1989). Several clinical trials have studied the use of prazosin in the treatment of benign prostatic hyperplasia. Five double-blind placebo-controlled trials have investigated the use of prazosin 2 mg twice daily; 4 of them demonstrated a significant increase in free urinary flow rate (Hedlund *et al.*, 1983; Martorana *et al.*, 1984; Kirby *et al.*, 1987; Hedlund and Andersson, 1988)

Table 3 Patients at Both Centres Reporting Reduced Frequency of Micturition

<i>Reduction</i>	<i>Treatment (total no.)</i>	<i>Mean baseline value</i>		<i>Responders</i>		<i>P*</i>
Voids/day	Prazosin (31) Placebo (36)	10.1 9.8		16 3		0.09
		Response				
		Yes		No		
		No.	%	No.	%	
Overall reduction	Prazosin Placebo	23 21	68 51	11 20	32 49	0.17

*Favouring prazosin treatment.

Table 4 Investigators' Overall Assessment of Efficacy of Treatment (Combined Data)

Treatment	No. assessing as: (% in parentheses)				Total no (%)
	Excellent	Good	Poor	None	
Prazosin	1 (3)	18 (53)	7 (21)	8 (24)	34 (100)
Placebo	1 (2)	8 (20)	18 (44)	14 (34)	41 (100)

P value in favour of prazosin HCL treatment = 0.02.

Note: Due to a rounding-off effect, the percentages for the prazosin group total more than 100.

Table 5 Investigators' Overall Assessment of Patients' Tolerance of Treatment

Treatment	No. assessing the relative risks of treatment as: (% in parentheses)				Total no (%)
	None	Not significant	Significant	Outweighing benefits	
Prazosin	14 (30)	18 (38)	3 (6)	12 (26)	47 (100)
Placebo	15 (34)	9 (21)	11 (25)	9 (21)	44 (100)

P value in favour of prazosin HCL treatment = 0.05.

Note: Due to a rounding-off effect, the percentages for the placebo group total more than 100

and the fifth demonstrated an increase which failed to reach statistical significance (Le Duc *et al.*, 1990). A double-blind study of prazosin 3 mg per day as contrasted to an amino acid preparation (Paraprost) demonstrated a significant improvement in flow rate on prazosin therapy (Yamaguchi *et al.*, 1990). None of these studies revealed any significant change in parameters of detrusor function during filling or voiding. Martorana *et al.* (1984) reported a significant reduction in the intraprostatic urethral pressure. Indeed, despite the evident efficacy of $\alpha 1$ adrenergic blockade in reducing the urethral closure pressure, review of the literature reveals that only a minority of the blinded placebo-controlled clinical studies of the efficacy of this therapy have demonstrated any significant effect on the urethral pressure profile. The most likely explanation for this apparent discrepancy lies in the methodological problems associated with the use of this technique in the conscious, unanaesthetised male patient.

No previous objective double-blind studies have investigated the use of prazosin over a time period in excess of 1 month. The majority of the existing short-term studies using prazosin have demonstrated that selective $\alpha 1$ adrenergic blockade can be effective with few adverse side effects. This report reviews the results of the first double-blind long-term study on the use of prazosin and has confirmed the observations of prior workers that there is an increase in the mean maximum urinary

flow rate on treatment. In addition, it provides the first evidence for a significant change in cystometric parameters, with a 19% reduction in maximum micturition pressure. The only other published long-term studies report the use of the selective $\alpha 1$ antagonist terazosin (Fabricius *et al.*, 1990; Lepor *et al.*, 1990; Lepor and Knapp-Maloney, 1991), indoramin (Iacovou and Dunn, 1987, Chow *et al.*, 1990) and alfuzosin (Ramsay *et al.*, 1985; Jardin *et al.*, 1991); with the exception of the work by Ramsay *et al.* (1985), which used videocystometry at entry and exit from the 3-month study, the other authors only studied patients' flow rates, post-voiding residual urine and symptom scoring, but did not evaluate other urodynamic parameters. Indeed, in the study reported by Jardin *et al.* (1991), only 45% of the patients had had a urinary flow rate estimation and only 36% a post-voiding residual urine prior to entry into the trial. The work reported by Ramsay *et al.* (1985) was the only one which failed to demonstrate any improvement in the urodynamic parameters of outflow obstruction. The other studies all demonstrated a significant increase in urinary flow rate which then decreased on continuing therapy by 1.3 ml/s (29.5%) (Lepor *et al.*, 1990), 0.6 ml/s (14.4%) (Fabricius *et al.*, 1990) and 1.8 ml/s (67%) (Jardin *et al.*, 1991) over a subsequent follow-up period of at least 13 weeks. In a subsequent open study of the longer-term use of terazosin, Lepor and Knapp-Maloney (1991)

Table 6 Adverse Events Considered Severe

<i>Treatment</i>	<i>Patient</i>	<i>Adverse event</i>	<i>Withdrawn</i>
Placebo	A204	Heartburn	Yes
	A209	Failure to ejaculate	No
	A219	Abdominal pain	Yes
	A223	Difficulty in micturition	Yes
	B36	Impotence, acute retention	No
Total number of severe adverse events		=6	
Total number of patients with severe adverse events		=5	
Total number of withdrawals due to adverse events		=3	
Prazosin	A202	Dizziness	Yes
	A207	Breathlessness, lightheadedness	Yes
	A221	Nausea	Yes
	A233	Blurred vision, dizziness	No
	B2	Abdominal pain	Yes
	B6	Malaise, headaches, lower abdominal pain	Yes
Total number of severe adverse events		=10	
Total number of patients with severe adverse events		=6	
Total number of withdrawals due to adverse events		=7	
(NB: In addition to those listed above, 2 patients were withdrawn for adverse events not considered severe, 1 at Centre A experiencing drowsiness and the other at Centre B exhibiting a rash and excessive sweating)			

Fig. Mean change from baseline in voiding parameters, maximum micturition pressure (cm H₂O) and maximum flow rate (ml/s) on placebo therapy compared with prazosin. The discrepancy in the numbers of patients (total no. = 71, although 75 completed the study) is attributed to missing results in a few individuals due to technical errors.

reported an increase in maximum flow rate of 4.7 ml/s at 6 weeks, reducing to 1.6 ml/s at 72 weeks. These observations are compatible with the development of tolerance to the effects of this drug therapy. However, the findings reported here support the alternative hypothesis that there is a dynamic rebalancing of the relationship between pressure and flow during voiding which results from α_1 blockade and that these effects on detrusor function take more than 1 month to occur. This would also explain why the increase in urinary flow rate was not as large as previously reported in a prior 1-month study using a similar protocol (Kirby *et al.*, 1987). Indeed, in support of this suggestion it is well recognised that the reduction in detrusor instability which occurs after prostatectomy may take up to 6 months. In view of the fixed time period of this study it is not possible to comment on whether the observed relationship between micturition pressure and flow was maintained at a longer follow-up period such as 6 months, but by inference from the terazosin studies which have data (not double-blinded) of up to 18 months (Lepor and Knapp-Maloney, 1991) this does seem likely.

The failure in this study to demonstrate significant subjective improvement in the urinary symptoms relating to the frequency and efficiency of

bladder emptying on active treatment is disappointing, since a major role of such therapy is to improve patients' symptomatology. A previous 1-month study investigating the therapeutic use of prazosin in the treatment of benign prostatic hyperplasia (Kirby *et al.*, 1987) revealed that a flow rate increase of less than 5 ml/s (unpublished observations) was not reported by patients as a subjective improvement. This provides a plausible explanation of the apparent disparity between failure of patients to report a subjective improvement in voiding function whilst on active therapy despite the ability of the investigators to predict under double-blind conditions which patients were on active therapy ($P=0.02$). A further factor which must be recognised in interpreting the results of this study is that the clinical symptomatology of benign prostatic hyperplasia may vary markedly over the course of time, and such a fluctuation occurring over a 3-month study period could mask changes resulting directly from the pharmacotherapeutic action of a drug. Nevertheless, the effect on detrusor function reported here is important because it is well recognised that in the long term, bladder and upper urinary tract damage may result from a chronic elevation of intravesical pressure.

The mechanism underlying the reduction in

voiding detrusor pressure documented here remains unknown. The possibilities are that it is the indirect consequence of a reduction in outflow resistance produced by a direct action on prostatic $\alpha 1$ receptors, or alternatively that it results from a direct effect on the α adrenoceptors within the detrusor (Perlberg and Caine, 1982); further experimental work is required to clarify this. It is of interest that a separate analysis of the results from centre B suggested that a more pronounced effect on detrusor voiding function was evident in the unstable bladder. This observation would favour the hypothesis relating "obstructive detrusor instability" to altered bladder adrenoceptor function and therefore supporting the latter concept, namely that prazosin has a direct pharmacological effect on the bladder. Unfortunately a similar combined analysis of data was not possible owing to differences between the 2 centres in defining low compliance and detrusor instability. The failure to document a significant change in any parameters of the urethral pressure profile does not militate against prazosin having a direct action on prostatic adrenoceptors. A similar observation has been made in the majority of previous studies and presumably this can be related to the well recognised methodological limitations and inaccuracies associated with urethral pressure profilometry.

The therapeutic effect of the $\alpha 1$ and $\alpha 2$ adrenoceptor antagonist phenoxybenzamine has been reported to be superior to that achieved by selective $\alpha 1$ blockade, presumably due to an additional action on $\alpha 2$ receptors. Human prostatic $\alpha 2$ adrenoceptors have been demonstrated using ligand binding studies (Hedlund *et al.*, 1985; Chapple *et al.*, 1989; Gup *et al.*, 1990) to be present in an increased density in patients with symptomatic benign prostatic enlargement. However, it seems unlikely that they subserve a significant motor role, since selective slide-mounted autoradiography studies of the human prostate have demonstrated them to be primarily localised to blood vessels and the basement membrane of glandular acini rather than to the stromal compartment which is the site of prostatic smooth muscle (James *et al.*, 1989).

These results suggest that prazosin needs to be given for a period longer than 1 month to achieve maximum benefit. The increase in urinary flow rate is not as great as might be expected and this can be partly attributed to a reduction in voiding detrusor pressure. Optimal pharmacological blockade of α receptors by producing a relaxation of prostatic smooth muscle is unlikely to produce >47% decrease in the total urethral closure pressure

(Furuya *et al.*, 1982), which is likely to be substantially less than that which could be obtained with surgical intervention. Laboratory studies need to be directed towards the search for more prostate-specific $\alpha 1$ receptor subtypes, which would allow the development of therapy which would produce fewer systemic side effects. Further clinical studies would use both comprehensive urodynamic assessment and the detailed analysis of changes in symptomatology; these should be directed at the investigation of the potential therapeutic efficacy of the concurrent use of selective $\alpha 1$ adrenergic blockade to relax prostatic smooth muscle combined with prostate selective hormonal blockade (e.g. 5 α -reductase inhibitors) to shrink the glandular tissue. Long-term treatment with selective $\alpha 1$ blockade using prazosin is safe, effective and produces changes in detrusor function which are an extension of the effect documented in previous short-term studies.

Acknowledgement

We thank Pfizer UK for supplying the materials which made this study possible.

References

- Abrams, P. H. (1985). Detrusor instability and bladder outlet obstruction. *Neurol. Urodynam.*, **4**, 317-328.
- Abrams, P., Blaivas, J. G., Stanton, S. L. *et al.* (1988). The standardisation of lower urinary tract function. *Scand J Urol. Nephrol (Suppl.)*, **114**, 5-19.
- Abrams, P. H., Shah, P. J. R., Stone, A. R. *et al.* (1981) Bladder outflow obstruction treated with phenoxybenzamine. *Prog. Clin. Biol. Res.*, **78**, 269-275.
- Abrams, P. H., Shah, P. J. R., Stone, A. R. *et al.* (1982). Bladder outflow obstruction treated with phenoxybenzamine. *Br. J. Urol.*, **54**, 527-530.
- Ball, A. J., Femeley, R. C. L. and Abrams, P. H. (1981). The natural history of untreated "prostatism". *Br. J. Urol.*, **53**, 613-616.
- Bartsch, G., Muller, H. R., Oberholzer, M. *et al.* (1979) Light microscopic stereological analysis of the normal human prostate and of benign prostatic hyperplasia. *J. Urol.*, **122**, 487-491.
- Bates, C. P., Whiteside, C. G. and Turner-Warwick, R. T. (1970) Synchronous cine/pressure/flow/cystourethrography with special reference to stress and urge incontinence. *Br. J. Urol.*, **42**, 714-723.
- Boreham, P. F., Braithwaite, P., Milewski, P. *et al.* (1977). Alpha-adrenergic blockers in prostatism. *Br. J. Surg.*, **64**, 756-757.
- Brooks, M. E., Siddi, A. A., Hanani, Y. *et al.* (1983). Ineffectiveness of phenoxybenzamine in treatment of benign prostatic hypertrophy. A controlled study. *Urology*, **21**, 474-478.
- Brown, M. and Wickham, J. E. A. (1969). The urethral pressure profile. *Br. J. Urol.*, **41**, 211-217.
- Caine, M. (1986). The present role of alpha-adrenergic blockers in the treatment of benign prostatic hypertrophy. *J. Urol.*, **136**, 1-4.

- Caine, M., Perlberg, S. and Meretyk, S. (1978). A placebo-controlled double-blind study of the effect of phenoxybenzamine in benign prostatic obstruction. *Br. J. Urol.*, **50**, 551-554.
- Caine, M., Pfau, A. and Perlberg, S. (1976). The use of alpha adrenoceptor blockers in benign prostatic obstruction. *Br. J. Urol.*, **48**, 255-263.
- Cambridge, D., Davey, M. J. and Massingham, R. (1977). Prazosin, a selective antagonist of post-synaptic alpha-adrenoceptors. *Br. J. Pharmacol.*, **59**, 514P-515P.
- Chapple, C. R., Aubry, M. L., James, S. *et al.* (1989). Characterisation of human prostatic adrenoceptors using pharmacology receptor binding and localisation. *Br. J. Urol.*, **63**, 487-496.
- Chow, W., Hahn, D., Sandhu, D. *et al.* (1990). Multicentre Controlled Trial of Indoramin in the Symptomatic Relief of Benign Prostatic Hypertrophy. *Br. J. Urol.*, **65**, 36-38.
- Donker, P. J., Ivanovici, F. and Noack, E. L. (1972). Analyses of the urethral pressure profile by means of electromyography and the administration of drugs. *Br. J. Urol.*, **44**, 180-193.
- Fabricius, P. G., Weizert, P., Dünzendorfer, U. *et al.* (1990). Efficacy of once-a-day terazosin in benign prostatic hyperplasia: a randomised placebo controlled clinical trial. *Prostate (Suppl. 3)*: 85-93.
- Furuya, S., Kumamoto, Y., Yokoyama, E. *et al.* (1982). Alpha-adrenergic activity and urethral pressure profilometry in prostatic zone in benign prostatic hypertrophy. *J. Urol.*, **128**, 836-839.
- Gerstenberg, T., Blaahjerg, J., Nielsen, M. L. *et al.* (1980). Phenoxybenzamine reduces bladder outlet obstruction in benign prostatic hyperplasia. A urodynamic investigation. *Invest. Urol.*, **18**, 29-31.
- Gup, D., Shapiro, E., Baumann, M. *et al.* (1990). Autonomic receptors in human prostate adenomas. *J. Urol.*, **143**, 179-185.
- Hedlund, H. and Andersson, K. E. (1988). Effects of prazosin and carbachol in patients with benign prostatic obstruction. *Scand. J. Urol. Nephrol.*, **22**, 19-22.
- Hedlund, H., Andersson, K. E. and Ek, A. (1983). Effects of prazosin in patients with benign prostatic obstruction. *J. Urol.*, **130**, 275-278.
- Hedlund, H., Andersson, K. E. and Larsson, B. (1985). Alpha-adrenoceptors and muscarinic receptors in the isolated human prostate. *J. Urol.*, **134**, 1291-1298.
- Iacovou, J. W. and Dunn, M. (1987). Indoramin—an Effective New Drug in the Management of Bladder Outflow Obstruction. *Br. J. Urol.*, **60**, 525-528.
- James, S., Chapple, C. R., Phillips, M. I. *et al.* (1989). Autoradiographic analysis of alpha-adrenoceptors and muscarinic cholinergic receptors in hyperplastic human prostate. *J. Urol.*, **142**, 438-444.
- Jardin, A., Bensadoun, H., Delauche-Cavallier, M. C. *et al.* (1991). Alfuzosin for treatment of benign prostatic hypertrophy. *Lancet*, **337**, 1457-1461.
- Kirby, R. S., Coppinger, S. W. C., Corcoran, M. O. *et al.* (1987). Prazosin in the treatment of prostatic obstruction: A placebo-controlled study. *Br. J. Urol.*, **60**, 136-142.
- Le Duc, A., Carliou, G., Baron, J. C. *et al.* (1990). A multicenter, double-blind, placebo-controlled study of the efficacy of prazosin in the treatment of dysuria associated with benign prostatic hypertrophy. *Urol. Int. (Suppl. 1)*, **45**, 56-62.
- Lepor, H. and Knapp-Maloney, G. (1991). Outcome assessment of terazosin for benign prostatic hyperplasia (BPH): 18 month follow-up. *J. Urol.*, **145**, 263A.
- Lepor, H., Knapp-Maloney, G. and Sunshine, H. (1990). A dose titration study evaluating terazosin, a selective, once-a-day α_1 -blocker for the treatment of symptomatic benign prostatic hyperplasia. *J. Urol.*, **144**, 1393-1398.
- Martorana, G., Gliberti, C., Damonte, P. *et al.* (1984). The effect of prazosin in benign prostatic hypertrophy: a placebo-controlled double-blind study. *IRCS Med. Sci.*, **12**, 11-12.
- Perlberg, S. and Caine, M. (1982). Adrenergic response of bladder muscle in prostatic obstruction. *Urology*, **20**, 524-527.
- Ramsay, J. W. A., Scott, G. I. and Whitfield, H. N. (1985). A double-blind controlled trial of a new α_1 blocking drug in the treatment of bladder outflow obstruction. *Br. J. Urol.*, **57**, 657-659.
- Straughan, J. L. (1978). Urinary incontinence with prazosin. *S. Afr. Med. J.*, **53**, 882.
- Thien, T., Delaere, K. P., Debruyne, E. M. *et al.* (1978). Urinary incontinence caused by prazosin. *Br. Med. J.*, **1**, 622-623.
- Wein, A. J. (1989). Prazosin in the treatment of prostatic obstruction. Editorial review. *J. Urol.*, **141**, 693-694.
- Yamaguchi, O., Shiraiwa, Y., Kobayashi, M. *et al.* (1990). Clinical evaluation of effects of prazosin in patients with benign prostatic obstruction. *Urol. Int. (Suppl. 1)*, **45**, 40-46.

The Authors

- C. R. Chapple, MD, FRCS, Senior Registrar, Middlesex Hospital.
- M. Stott, MD, FRCS, Senior Registrar, Ham Green Hospital.
- P. H. Abrams, MD, FRCS, Consultant Urologist, Ham Green Hospital.
- T. J. Christmas, FRCS, Urodynamic Research Fellow, Middlesex Hospital.
- E. J. G. Milroy, FRCS, Consultant Urologist, Middlesex Hospital.

Requests for reprints to: C. R. Chapple, Department of Urology, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF

Prostate Specific Antigen and Bone Scan Correlation in the Staging and Monitoring of Patients with Prostatic Cancer

P. D. MILLER, I. EARDLEY and R. S. KIRBY

Department of Urology, St Bartholomew's Hospital, London

Summary—The ability of serum prostate specific antigen (PSA) to predict bone metastases at initial presentation was determined in 146 patients, and in 66 patients during a 3-year period; 14.7% of patients with bone metastases at presentation had a PSA value less than 20 ng/ml. All patients who subsequently developed bone metastases had a PSA greater than 20 ng/ml and the rise in PSA often antedated the detection of bone metastases. Bone scans are still necessary in the initial staging but following diagnosis and treatment can be replaced by serum PSA measurement in monitoring patients with prostatic cancer.

Prostate specific antigen (PSA) is a glycoprotein with a molecular weight of 34,000 daltons; it is excreted exclusively by prostatic epithelial cells and was first isolated in 1979 by Wang *et al.* Several commercial assays are now available and this has largely replaced the measurement of prostate acid phosphatase (PAP), as PSA has been shown to be considerably more sensitive as a tumour marker in all stages of prostate cancer (Myrtle *et al.*, 1986). The exact role of PSA in urological practice has yet to be fully evaluated, but several reports suggest that it is most suited to monitoring response to therapy. Bone scanning is a sensitive (but not very specific) means of detecting skeletal metastases from prostatic carcinoma and may precede radiographic detection by 3 to 6 months. However, any reduction in the routine use of this relatively expensive and time-consuming procedure in staging and monitoring patients with prostatic carcinoma would be of significant benefit.

This study was designed to ascertain the ability of PSA to predict the presence of bony metastases at the time of original diagnosis of prostate cancer and their development during follow-up of these patients.

Patients and Methods

Serum levels of PSA were evaluated at the time of diagnosis in all patients with histologically proven carcinoma of the prostate presenting over a 3-year period ($n = 146$). All patients were clinically staged prior to any treatment. Staging included whole body bone scintigraphy and the images were interpreted and reported by an experienced radiologist. Subsequently, 66 patients who had negative bone scans at the time of diagnosis were followed up with repeated PSA estimations at least every 6 months for 6 to 36 months (mean 19). These patients were treated variously with radiotherapy, radical retropubic prostatectomy, orchiectomy and some by transurethral resection alone. Further bone scans were performed if there was clinical evidence of metastases. PSA values were compared with the bone scan results and assessed with respect to positive and negative predictive values for determining bone metastases.

Positive predictive value (PPV) = percentage of patients with PSA beyond a predetermined limit who were bone scan positive. Negative predictive value (NPV) = percentage of patients with PSA below predetermined limit who were bone scan negative.

Serum PSA assays were determined using the

Tandem PSA-R assay (Hybritech Inc.), a solid phase two site immunoradiometric assay (cut off level = 4 ng/ml) with excellent intra-assay reproducibility ($cv = 1.3-3.0$) (Chan *et al.*, 1987). Whole body bone scintigraphy was performed using ^{99m}Tc labelled methylene diphosphonate.

Results

Data at initial presentation (146 patients)

Thirty-four patients (23%) had bone metastases at initial presentation; 3 of these (9%) had PSA values within the normal range (< 4 ng/ml). However, the majority of these patients (71%) had very high PSA values, well in excess of 20 ng/ml (Table 1). It was interesting to find as many as 5 patients in this series with low PSA values (< 10 ng/ml) with known bone metastases (Fig. 1), although this has been reported before in other series (Siddall *et al.*, 1986). The positive predictive values at 10 ng/ml (33%) and 20 ng/ml (38%) are poor, and the negative predictive values at similar cut-off levels for skeletal metastases show that PSA alone would have failed to detect a significant number of patients who already had bone metastases at presentation (Table 2).

Table 1 Levels of Serum PSA at Presentation and Tumour Category

Tumour category	PSA (ng/ml)			
	0-4.0	4.01-10	10.01-20	> 20
T0-2	18	14	7	3
T3-4	15	5	14	36
T0-4 + bone metastases	3	2	5	24

Table 2 Predictive Value of PSA Determining Bone Metastases at Initial Presentation

PSA (ng/ml) cut-off value	PPV	NPV
> 10	33% (29/89)	91% (52/57)
> 20	38% (24/63)	88% (73/83)

Data at follow-up (66 patients)

During the follow-up period 11 patients (17%) became bone scan positive. All of these patients were found to have elevated PSA levels > 20 ng/ml (Table 3). Therefore a cut-off value of 20 ng/ml for

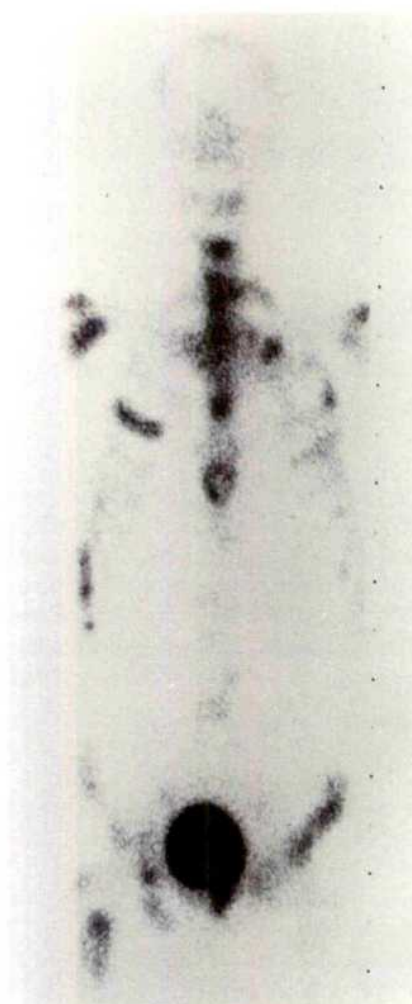


Fig. 1 Isotope bone scan performed at presentation showing wide-spread skeletal metastases in a patient with a serum PSA of 6.8 ng/ml.

Table 3 Levels of Serum PSA at Follow-up (mean 22 months) of 66 Patients who had Negative Bone Scans at Presentation

Bone scan	PSA (ng/ml)			
	0-4.0	4.01-10	10.01-20	> 20
No metastases	20	16	9	10
Bone metastases	0	0	0	11

skeletal metastases would give a positive predictive value in this group of patients of 53% and a negative predictive value of 100% (Table 4).

In 4 of the patients who developed bone metastases, a rising PSA up to 100 ng/ml antedated

bone scan evidence of metastases by up to 6 months (Fig. 2).

Table 4 Predictive Value of PSA Determining Bone Metastases during Follow-up of 66 Patients

PSA (ng/ml) cut-off value	PPV	NPV
> 10	37% (11/30)	100% (36/36)
> 20	53% (11/21)	100% (45/45)

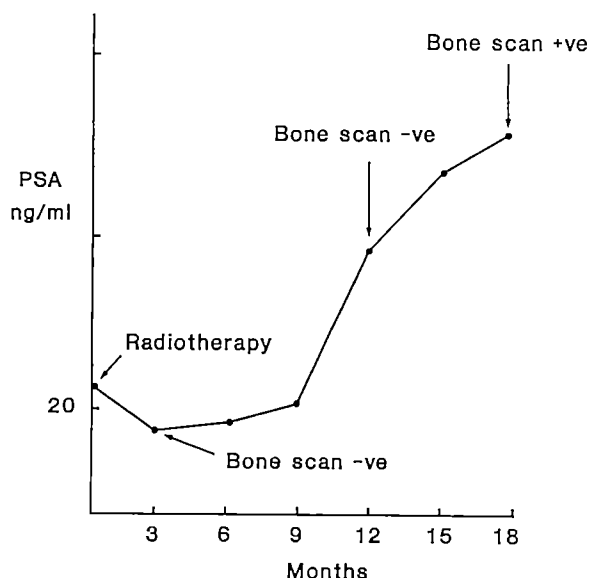


Fig. 2 Changes in serum PSA values in patient with localised prostatic carcinoma following radiotherapy. PSA rise antedates bone scan detection of metastases by 6 months.

Discussion

PSA has been used in the management of patients with prostatic carcinoma in an attempt to stage the disease, particularly in patients prior to radical prostatectomy (Stamey *et al.*, 1989). Myrtle *et al.* (1986) have shown PSA to be a much more sensitive marker than prostate acid phosphatase, with a good correlation between the stage of the disease and the proportion of patients with increased serum levels. However, several series have shown that there is considerable overlap between various pathological stages (Oesterling *et al.*, 1988; Hudson *et al.*, 1989; Lange and Brawer, 1989), such that PSA alone is unreliable for accurate staging.

At initial presentation our data confirm these observations and also show that if PSA was used

alone for staging, a proportion of patients with bone metastases would be missed (Table 1). A recent review (Shearer, 1991) quotes the negative accuracy for a PSA level of 20 ng/ml to be 92%, with the conclusion that patients with PSA levels of 20 ng/ml or less do not require bone scans. Despite a PSA of less than 10 ng/ml, the presence of bone metastases was reported in bone scans of 5 of the 34 patients in our series, although bone biopsy was not performed to confirm these findings (Fig. 1). Similar reports (Siddall *et al.*, 1986) show that PSA alone is inadequate for staging, particularly with poorly differentiated prostatic carcinoma which does not express PSA. Bone scintigraphy must therefore still be advocated as part of the initial staging procedure.

The ability of PSA to predict disease progression has been demonstrated by Ercole *et al.* (1987), who showed that the median interval between elevation of PSA and evidence of disease progression was 6 months. Kuriyama *et al.* (1981) also showed that serum levels of PSA corresponded accurately with clinical status in advanced disease progression in patients with localised disease following therapy. Although repeated bone scans have been advocated in the assessment of treatment response in carcinoma of the prostate (Fitzpatrick *et al.*, 1978), our results suggest that with the advent of PSA this is unnecessary. With a relatively low cut-off level of PSA of 20 ng/ml, this would give a negative predictive value of 100% for detecting bone metastases during disease follow-up (*i.e.* 100% of our patients who developed bone metastases during this period had a PSA > 20 ng/ml). This value may be too low for routine use and further studies are needed to clarify the most useful cut-off value, although our findings using this level support those of similar series (Bowman *et al.*, 1990). The high sensitivity of PSA facilitating the early detection of bone metastases and the importance of a rising titre with serial measurements have been reported by Fincker *et al.* (1988). Killian *et al.* (1985) showed a progressive elevation in PSA following radical prostatectomy in 6 patients who subsequently developed positive bone scans. Furthermore, PSA antedated bone scan evidence of metastatic disease by 12 to 43 months, and there was further evidence of this in our series (Fig. 2).

There can be no doubt that PSA is an excellent marker for disease progression in prostate cancer and that it can be used to monitor disease activity following initial staging, whether followed by primary treatment or a conservative approach. Our evidence, along with other data, suggest that it may

replace the need for serial bone scan and other progression monitors. This will be a considerable advantage not only to the elderly patient who will avoid a lengthy isotope scan but also to our health resources.

Acknowledgements

We thank Mrs Andrea Brown, Department of Chemical Pathology, who performed the assays and helped to record and analyse the data.

References

- Bowman, S., Pantelides, M. and George, N. J. R. (1990). PSA identification of localised cancer with low biological potential in the elderly male. *J. Urol. (6 Suppl.)*, **143**, 71.
- Chan, D. W., Bruzek, D. J., Oesterling, J. E. *et al.* (1988). Prostate specific antigen as a marker for prostate cancer: a monoclonal and polyclonal immunoassay compared. *Clin. Chem.*, **33**, 1916–1920.
- Ercole, C. J., Lange, P. H., Mathiesen, M. *et al.* (1987). Prostate specific antigen and prostatic acid phosphatase in the monitoring and staging of patients with prostatic cancer. *J. Urol.*, **138**, 1181–1184.
- Fincker, M. D., Sauvan, R. and Pasquier, J. (1988). Systematic association of PAP and PSA determinations in bone scintigraphy in prostatic cancer. *Am. J. Clin. Oncol.*, **11**, 68–70.
- Fitzpatrick, J. M., Constable, A. R., Sherwood, T. *et al.* (1978). Serial bone scanning: the assessment of treatment response in carcinoma of the prostate. *Br. J. Urol.*, **50**, 555–561.
- Hudson, M. A., Bahnson, R. R. and Catalona, W. J. (1989). Clinical use of prostate specific antigen in patients with prostate cancer. *J. Urol.*, **142**, 1011–1017.
- Killian, C. S., Yang, N., Emrich, L. J. *et al.* (1985). Prognostic importance of prostate-specific antigen for monitoring patients with stage B2 to D1 prostate cancer. *Cancer Res.*, **45**, 886–891.
- Kuriyama, M., Wang, M. C., Lee, C. I. *et al.* (1981). Use of human prostate-specific antigen in monitoring prostate cancer. *Cancer Res.*, **41**, 3874–3876.
- Lange, P. H. and Brawer, M. K. (1989). Serum prostate specific antigen: its use in the diagnosis and management of prostate cancer. *Urology (6 Suppl.)*, **33**, 13–17.
- Myrtle, J. F., Klimey, P. G., Ivor, L. P. *et al.* (1986). Clinical utility of prostate-specific antigen (PSA) in the management of prostate cancer. *Adv. Cancer Diag., Hybritech Inc.*, 1–9.
- Oesterling, J. E., Chan, D. W., Epstein, J. I. *et al.* (1988). Prostate specific antigen in the preoperative and postoperative evaluation of localised prostatic cancer treated with radical prostatectomy. *J. Urol.*, **139**, 766–772.
- Shearer, R. J. (1991). Prostatic specific antigen. *Br. J. Urol.*, **67**, 1–5.
- Siddall, J. K., Cooper, E. H., Newling, D. W. *et al.* (1986). An evaluation of the immunochemical measurement of prostatic acid phosphatase and prostate specific antigen in carcinoma of the prostate. *Eur. Urol.*, **12**, 123–130.
- Stamey, T. A., Kabalin, J. N., McNeal, J. E. *et al.* (1989). Prostatic specific antigen in the diagnosis and treatment of adenocarcinoma of the prostate. II. Radical prostatectomy treated patients. *J. Urol.*, **141**, 1076–1083.
- Wang, M. C., Valenzuela, L. A., Murphy, G. P. *et al.* (1979). Purification of a human prostate specific antigen. *Invest. Urol.*, **17**, 159–163.

The Authors

P. D. Miller, BSc, FRCS, Senior Registrar.
I. Eardley, MA, FRCS, Senior Registrar.
R. S. Kirby, MA, MD, FRCS, Consultant Urologist.

Requests for reprints to: P. D. Miller, Department of Urology, Royal United Hospital, Combe Park, Bath BA1 3NG.

Levels of Prostate Specific Antigen that Predict Skeletal Spread in Prostate Cancer

M. L. PANTELIDES, S. P. BOWMAN and N. J. R. GEORGE

University Department of Urology, Withington Hospital, Manchester

Summary—The ability of serum prostate specific antigen (PSA) and serum acid phosphatase (SAP) to identify skeletal spread was evaluated in untreated patients with prostatic cancer. Twenty patients with scintigraphic evidence of metastatic disease in bone (M1) at diagnosis were compared with 50 untreated patients in whom scans were repeatedly negative during long-term surveillance. Using the present laboratory upper limit of normal (ULN) of 3 iu/l, the sensitivity and specificity of SAP for M1 disease were 80 and 86% respectively. Stepwise discriminant analysis demonstrated that SAP was able to stage patients correctly (bone scan positive or negative) with 81% predictive accuracy at an optimum cut-off limit of 4.6 iu/l. By contrast, whilst PSA (Hybritech) was 100% sensitive for skeletal disease at 10 ng/ml—at the expense of poor (36%) specificity—analysis determined that an optimum cut-off limit of 58 ng/ml led to 79% predictive accuracy for disease in bone. It was concluded that PSA levels > 58 ng/ml are highly indicative of spread to the skeleton, even in the absence of radiological or scintigraphic evidence of metastases.

The prognosis and survival of patients with prostate cancer are recognised to depend significantly upon whether or not skeletal metastatic disease can be identified at the time of diagnosis (Lund *et al.*, 1984; George, 1988).

The finding of raised levels of serum acid phosphatase (Gutman and Gutman, 1938) has for many years assisted in the identification of such patients and despite the recognition that normal values may be found in a minority of patients with bony disease (Heller, 1987), elevated levels of the enzyme may, particularly in the presence of negative ⁹⁹Tc scintigraphy, provide warning of tumour dissemination and thus prevent inappropriate treatment being offered to patients with occult metastatic disease.

Serum prostate specific antigen (Wang *et al.*, 1979) is, by contrast, raised in patients with both local and metastatic prostate carcinoma and this increased sensitivity (Ahmann and Schiffman, 1987) has been found to be of great assistance for monitoring clinical progress and response to medi-

cal (Siddall *et al.*, 1986) or surgical (Stamey *et al.*, 1989) treatment. However, whilst increased sensitivity has led many laboratories to consider replacing SAP by PSA, there is concern regarding the specificity of serum PSA in identifying skeletal spread. The lack of objective data concerning the cut-off limits of PSA that could discriminate between non-skeletal and skeletal disease may seriously hamper the urologist wishing to advise his patient regarding appropriate therapy and likely progress of the disease.

This study has therefore analysed data from untreated patients with and without skeletal disease in order to compare the ability of SAP and serum PSA to provide such clinically useful cut-off limits.

Patients and Methods

Seventy patients with untreated but histologically confirmed prostate cancer were admitted to the study and 20 of these had unequivocal scintigraphic and radiological evidence of skeletal disease (M1) when assessed immediately prior to institution of hormonal manipulation therapy. Fifty patients had neither clinical nor bone scan evidence of spread;

34 of these (68%) were digitally staged T0–T2 and 43 (86%) had moderately or well differentiated tumours on histological examination. A deferred treatment policy in this group of 50 patients (follow-up: range 6–127, mean 47, median 56 months) ensured that all patients had multiple clinical assessments (including repeatedly negative bone scans) up to the time of recruitment to the study.

Blood was taken prior to rectal assessment, prostatic biopsy or transrectal ultrasound in all cases. Serum was extracted and stored without delay at -20°C prior to analysis. PSA solid phase immunoradiometric assays were performed in batches using commercially available kits (Tandem-R, Hybritech) with acceptable within and between assay precision, according to the manufacturers' instructions. Enzymatic SAP assays were analysed routinely using alpha-naphthylphosphate as substrate and tartrate inhibition. Discriminant analysis was performed as described by Armitage and Berry (1987).

Results

The SAP levels in the 2 groups of patients with prostate cancer are shown in Figure 1. Values in 20 patients with positive bone scans ranged widely (range 0.7–1100, mean 90.2 ± 264 , median 13 iu/l) and in 16 of these patients the values were greater than 3 iu/l, giving a sensitivity for the test of 80% at this specified upper limit of normal (ULN) used in this laboratory.

Repeated SAP measurements during follow-up of 43 of the 50 patients without scintigraphic changes remained within normal limits (<3 iu/l), demonstrating a test specificity for M1 disease of 86%. None of these patients developed positive bone scans during the study. Seven patients (Fig. 1) with initially negative bone scans had markedly raised SAP (range 7.4–43, mean 15, median 8 iu/l) which continued to elevate during the study period, leading to designation as category MX; of these, 3 have since progressed to overt skeletal metastases during a mean follow-up of 10.8 months.

Mean PSA values tended to increase with increasing local category ($\text{T0} = 42 \pm 67$ ng/ml; $\text{T1} + 2 = 47 \pm 115$ ng/ml; $\text{T3} = 81 \pm 127$ ng/ml; $\text{M1} = 863 \pm 1565$ ng/ml (means $\pm$ SD)) (Fig. 2). However, owing to the large scatter the only significant difference was between the non-skeletal and skeletal metastatic groups of patients ($P < 0.005$).

There was a wide spread of PSA values in the bone scan negative group of patients (Fig. 3) (Table). A total of 32 patients had PSA levels

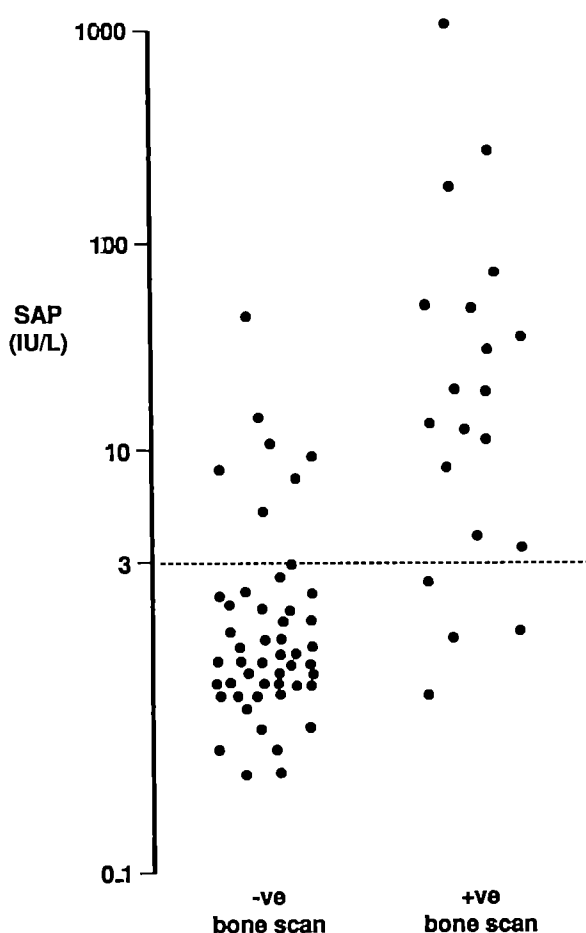


Fig. 1 Serum acid phosphatase levels in patients with positive bone scans (M1, $n=20$) and those with clinically localised cancers (M0, $n=50$).: ULN in hospital laboratory.

>10 ng/ml, the widely adopted ULN for benign hyperplasia (BPH), giving a sensitivity of 64% and a correspondingly low specificity (36%) for distant disease spread; 23 patients had PSA levels <20 ng/ml. Levels in patients with skeletal metastases were considerably higher and although overlap with results from the bone scan negative group was observed, this was not extensive when results from the 7 equivocal MX patients were taken into account (Fig. 3).

Table Numerical Values of PSA as Illustrated in Figure 3

	No	Range (ng/ml)	Mean ($\pm$ 1SD) (ng/ml)	Median (ng/ml)
BPH	20	1–21	6 ± 6	5
M0	50	1–550	53 ± 103	16
M1	20	30–6300	863 ± 1565	197

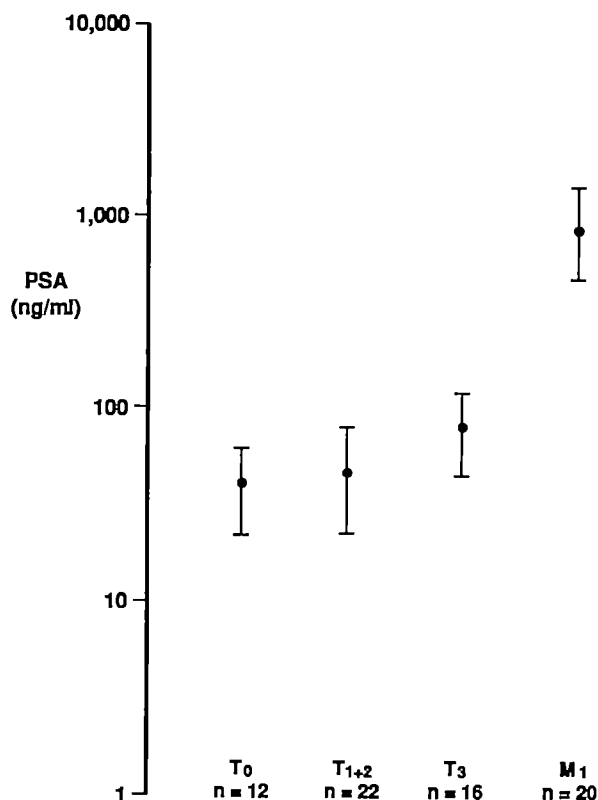


Fig. 2 PSA levels (Hybritech) in the various local stages of patients with negative bone scans and in the group with skeletal spread. Bars: mean $\pm$ 1SD.

Stepwise discriminant analysis was used to determine the optimum cut-off limits of serum PSA and SAP that would distinguish between the 2 groups of patients, excluding those with MX disease. Overall, SAP was able to stage patients correctly, *i.e.* whether bone scan positive or negative, with an 81% predictive accuracy at an optimum cut-off of 4.6 iu/l. The corresponding predictive accuracy of PSA was insignificantly worse at 79% at an optimum cut-off of 58 ng/ml (Fig. 3).

Discussion

Tumour markers may be used for screening, monitoring or staging patients with malignant disease. The advent of PSA (Wang *et al.*, 1979) has caused a widespread reappraisal of the role of serum markers in prostate cancer; in this study the ability of serum PSA correctly to stage M1 disease (patients with skeletal metastases) has been examined and compared with the "standard" SAP method introduced 50 years ago (Gutman and Gutman, 1938).

Valid comparisons between groups of patients demand that each is characteristic of its type. Whilst 20 patients had definite evidence of bony metastatic disease (untreated at time of study), 50 patients with repeatedly negative scintigraphy had been followed up on a deferred treatment policy for a number of years. In this way possible false negative classification errors caused by "single scan" evaluations were avoided and the stability of the non-skeletal group was guaranteed as far as possible by consistent observations made over an extended period of time; thus 7 patients with markedly raised SAP were reclassified as equivocal metastatic status (MX), as it is recognised that many such patients may harbour latent skeletal metastatic disease (Prout, 1973).

Serum acid phosphatase was confirmed as a

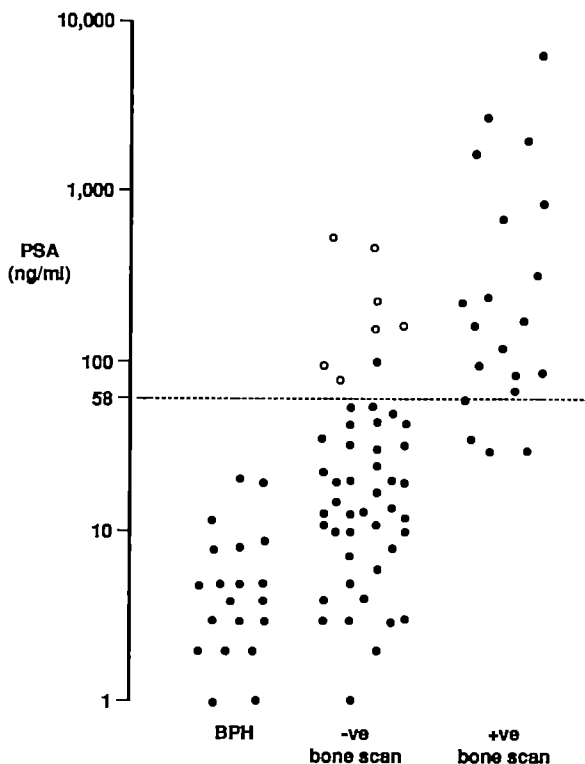


Fig. 3 PSA levels in groups of patients with bone scan positive (M1) and scan negative (M0) disease. (o): PSA values in the 7 patients whose SAP levels were markedly elevated over the laboratory ULN, as illustrated in Figure 1. (...): optimum cut-off level of PSA for metastatic disease in bone. For comparison, values from 20 routine patients with clinical and histological evidence of benign prostatic hyperplasia are illustrated. Effective discrimination between prostatic cancer and benign prostatic hyperplasia was possible using a ULN of 10 ng/ml, giving an 85% specificity and 64% sensitivity for non-metastatic disease, a result similar to that of Ferro *et al.* (1987).

sensitive indicator of bony disease and this finding is in broad agreement with many other series reviewed by Heller (1987). Elevated levels in the absence of a positive bone scan are confirmed as heralding impending bony invasion and the adverse prognostic implication of this sign has been noted in patients treated by both radiation therapy (Babaian and Orlando, 1986) and radical prostatectomy (Bahson and Catalona, 1987). However, the large number of different SAP assays and the arbitrary limits of normality employed have led to criticisms of its usefulness and highlight the need for optimising cut-off limits by clinical evaluation at each individual centre. This study has revealed that an upper limit of normal of 4.6 iu SAP was better at diagnosing skeletal spread than the level of 3 iu previously used, with only a small (2%) reduction in clinical sensitivity.

Prostate specific antigen is a marker of prostatic epithelial tissue and as such is raised in patients with all forms of prostatic enlargement. It seems likely that the poor correlation observed between PSA levels and clinical (essentially digital) tumour assessment (Fig. 2) was a reflection of imprecise staging. The initial hope that PSA would accurately reflect tumour volume and discriminate between different local stages has not been sustained as a result of sophisticated studies conducted after radical prostatectomy; whereas Stamey *et al.* (1989) reported a direct correlation between tumour volume and PSA values ($r=0.70$), others have found a less satisfactory link ($r=0.535$) between the 2 variables (Partin *et al.*, 1990). It is probable that PSA levels fail to reflect local disease burden accurately owing to the variable amount of benign tissue present and heterogeneous antigenic expression of PSA-producing tumour clones as evidenced both in established human prostatic carcinoma lines (Papsidero *et al.*, 1981) and the patchy immunohistochemical PSA staining of tumour tissue (Epstein and Eggleston, 1984).

Whilst increased sensitivity is clinically useful for monitoring progress in elderly patients with histologically proven localised prostate cancer, the lack of an established "cut-off" for skeletal disease is a drawback for the surgeon, who would not wish to offer inappropriate therapy for bone scan negative patients who might be at imminent risk of scan conversion. This problem is compounded by the withdrawal of SAP assays and substitution of PSA assays by many clinical laboratories. Discriminant analysis in the 2 closely defined groups of patients studied (excluding 7 MX patients) demonstrated a limit of 58 ng/ml (79% predictive accuracy)

to be the optimum cut-off that distinguished between skeletal and non-skeletal disease. Hence, patients with normal scintigraphy but PSA levels above this value are likely to have incipient bony disease. It is noteworthy that the predictive accuracy of SAP for metastatic disease was marginally greater (81%) at an optimum cut-off of 4.6 iu/l.

Patients in this study did not undergo staging laparotomy or other manoeuvres that could reliably demonstrate between confined intracapsular cancers and disease which had spread to lymph nodes. It is thus impossible to comment precisely on the significance of the range of PSA values found in the patients without skeletal disease. Partin *et al.* (1990) observed PSA levels >10 ng in 6/24 patients (25%) with seminal vesicle involvement and 22/54 (41%) with positive pelvic node biopsies. The greater proportion of M0 patients in the present series with PSA values between 10 and 58 ng is likely to represent the increased number of UK patients who present late to their physician (possible greater tumour burden in soft tissue) as compared to patients in the USA.

Whilst it might be argued that all PSA levels above those related to truly localised disease (*i.e.* disease suitable for radical prostatectomy or X-ray therapy) are of academic interest only, since hormone manipulation will be required whether or not disease has spread to bone, a number of authors have noticed increased survival in treated patients with N1 M0 (D1) disease (Zinke *et al.*, 1987; Sandhu *et al.*, 1990; Steinberg *et al.*, 1990) when compared with the typically poor outlook (50% 2-year, 13% 5-year survival) (George, 1988) of patients with skeletal spread. Hence the knowledge of where an individual PSA value lies in the "D1 range"—10/15–58 ng/ml—may be extremely helpful for a surgeon advising his patient on the degree and prognosis of his individual disease.

In summary, despite its sensitivity and an overlap of values between metastatic and non-metastatic groups of patients, serum PSA has been found able to identify prostate cancer patients with skeletal spread using an upper limit of normal of 58 ng/ml. Whilst the conventional SAP assay still remains the "gold standard" as a cost-effective indicator of skeletal metastatic status, PSA values in the range below the cut-off value are of useful prognostic value in patients whose disease has escaped the boundaries of the prostate gland itself.

Acknowledgements

We thank Dr R. Swindell for statistical assistance and Mrs G. Trimble for typing the manuscript.

References

- Abmaun, F. R. and Schiffman, R. B. (1987). Prospective comparison between serum monoclonal prostate specific antigen and acid phosphatase measurements in metastatic prostatic cancer. *J. Urol.*, **137**, 431–434.
- Armitage, P. and Berry, G. (1987). Multiple measurements. In *Statistical Methods in Medical Research*. Second edition. Chapter 10, pp. 334–341. Oxford: Blackwell.
- Babayan, R. J. and Orlando, R. P. (1986). Elevated prostatic acid phosphatase: a prognostic factor for stage C adenocarcinoma of the prostate. *J. Urol.*, **136**, 1035–1037.
- Babson, R. P. and Catalona, W. J. (1987). Adverse implications of acid phosphatase levels in the upper range of normal. *J. Urol.*, **137**, 427–430.
- Epstein, J. I. and Eggleston, J. C. (1984). Immunohistochemical localisation of prostate-specific acid phosphatase and prostate-specific antigen in stage A2 adenocarcinoma of the prostate: prognostic implications. *Hum. Pathol.*, **15**, 853–859.
- Ferro, M. A., Barnes, I., Roberts, J. B. M. *et al.* (1987). Tumour markers in prostatic carcinoma. A comparison of prostate-specific antigen with acid phosphatase. *Br. J. Urol.*, **60**, 69–73.
- George, N. J. R. (1988). Natural history of localised prostatic cancer managed by conservative therapy alone. *Lancet*, **1**, 494–496.
- Gutman, A. B. and Gutman, E. B. (1938). An "acid" phosphatase occurring in the serum of patients with metastasizing carcinoma of the prostate gland. *J. Clin. Invest.*, **17**, 473–478.
- Heller, J. E. (1987). Prostatic acid phosphatase. its current clinical status. *J. Urol.*, **137**, 1091–1103.
- Lund, F., Smith, P. H., Sochi, S. *et al.* (1984). Do bone scans predict prognosis in prostatic cancer? *Br. J. Urol.*, **56**, 58–63.
- Papsidero, J. D., Kuriyama, M., Wang, M. C. *et al.* (1981). Prostate antigen: a marker for human prostate epithelial cells. *J. Natl. Cancer Inst.*, **66**, 1, 37–41.
- Partin, A. W., Carter, H. B., Chan, D. W. *et al.* (1990). Prostate specific antigen in the staging of localised prostate cancer; influence of tumour differentiation, tumor volume and benign hyperplasia. *J. Urol.*, **143**, 747–752.
- Prout, G. R. (1973). Diagnosis and staging of prostatic carcinoma. *Cancer*, **32**, 1096–1103.
- Sandhu, D. P. S., Mayor, P. E., Sambrook, P. *et al.* (1990). Increased survival of patients with massive lymphadenopathy and prostate cancer: evidence of herogeneous tumour behaviour. *Br. J. Urol.*, **66**, 415–419.
- Siddall, J. K., Hetherington, J. W., Cooper, E. H. *et al.* (1986). Biochemical monitoring of carcinoma of prostate treated with an LH-RH analogue (Zoladex). *Br. J. Urol.*, **58**, 676–682.
- Stamey, T. A., Kabalin, J. N., McNeal, J. E. *et al.* (1989). Prostatic specific antigen in the diagnosis and treatment of adenocarcinoma of the prostate II Radical prostatectomy treated patients. *J. Urol.*, **141**, 1076–1083.
- Steinberg, G. D., Epstein, J. I., Piantadosi, S. *et al.* (1990). Management of stage D1 adenocarcinoma of the prostate: the Johns Hopkins experience 1974 to 1987. *J. Urol.*, **144**, 1425–1432.
- Wang, M. C., Valenzuela, L. A., Murphy, G. P. *et al.* (1979). Purification of a human prostate specific antigen. *Invest. Urol.*, **17**, 159–163.
- Zincke, H., Utz, D. C., Thule, P. M. *et al.* (1987). Treatment options for patients with stage D1 (T0–3, N1–2, M0) adenocarcinoma of the prostate. *Urology*, **30**, 307–311.

The Authors

- M. L. Pantelides, MD, FRCS, Senior Registrar in Urology, Stepping Hill Hospital.
- S. P. Bowman, MSc, Research Biochemist, Department of Urology, Withington Hospital.
- N. J. R. George, MD, FRCS, Senior Lecturer, Consultant in Urology, Withington Hospital

Requests for reprints to: M L Pantelides, Department of Urology, Stepping Hill Hospital, Stockport SK2 7JE.

Treatment of Advanced Localised Prostatic Cancer by Orchiectomy, Radiotherapy, or Combined Treatment. A Medical Research Council Study

G. J. FELLOWS, P. B. CLARK, L. L. BEYNON, J. BOREHAM, C. KEEN, M. C. PARKINSON,
R. PETO and J. N. WEBB

(Urological Cancer Working Party—Subgroup on Prostatic Cancer)

Summary—A total of 277 patients with apparently localised prostatic cancer (T2–T4 NXMO) were allocated at random to receive radiotherapy alone (88), orchiectomy alone (90) and combined therapy (99) between 1980 and 1985. The main outcome measures were survival, time to appearance of metastases and treatment of local disease progression by further transurethral resection. Orchiectomy, whether alone or with radiotherapy, produced a significant delay in detection of metastases when compared with radiotherapy alone. There were no statistically significant differences between the 3 treatment groups in local disease control or in overall survival.

There is no consensus as to how apparently localised prostatic cancer should be treated. If the disease is really localised then radical prostatectomy or radiotherapy can be curative (Lepor and Walsh, 1988; Hanks, 1989). Only the latter has been practised on a large scale in the United Kingdom. Systemic therapy with cytotoxic agents does not appear to be particularly effective, but systemic hormonal therapy can often lead to prolonged regression of the primary tumour and hence palliation of its local effects (Schröder, 1990). The hormonal therapies now available include bilateral orchiectomy, oestrogens, anti-androgens and LH-RH analogues. At the end of the 1970s, however, LH-RH analogues and anti-androgens were not widely available, oestrogens were known to produce cardiovascular complications and orchiectomy was therefore the standard hormonal treatment. No randomised trial of radiotherapy versus hormonal treatment had been performed. In 1980, at the suggestion of one of the authors (P.B.C.), the Medical Research Council therefore launched a multi-centre randomised trial of orchiectomy versus radiotherapy versus combined treatment (orchiectomy and radiotherapy) in advanced localised (T2–T4 NXMO) prostatic cancer.

The object was to compare the effects of these 3 treatments on the duration of survival and on the time to appearance of metastases.

Patients and Methods

All patients had histologically proven carcinoma of the prostate. Sections were reviewed by 2 pathologists and ascribed a Gleason score. No patient had prior hormonal treatment or radiotherapy: surgery to relieve outflow obstruction was, however, permitted. There had to be no evidence of metastases on chest X-ray or isotope bone scan. Lymph node staging was not required. Patients were excluded if the serum acid phosphatase was above the upper limit of normal for the local laboratory. The patient's performance status was recorded.

The treatment group was allocated randomly, without stratifying for any possible prognostic variables, by telephoning the ICRF/MRC Clinical Trial Service Unit in Oxford. Orchiectomy could be total or subcapsular according to local preference. Radiotherapy involved a radical course of treatment to the prostate gland, the actual technique

being left to the discretion of the individual radiotherapist.

The design of the trial was deliberately kept as simple as possible so as not to impose an undue burden on elderly patients and to encourage as many surgeons as possible to participate. Patients were to be reviewed every 6 months until death for clinical evidence of local progression or distant metastases and for assessment of any major adverse reactions to therapy. Isotope bone scans and chest X-rays were to be performed annually or whenever metastases were suspected. Patients who died from prostatic cancer were assumed to have developed metastases midway between latest symptom-free follow-up and death if no date of onset had been reported.

Thirty-two urologists in 23 centres entered a total of 277 patients into the trial between June 1980 and March 1985. Ninety patients were allocated orchiectomy alone, 88 radiotherapy alone and 99 combination therapy. The 3 groups were roughly comparable (Table 1) regarding age, performance status, T category and Gleason score and were

followed up for comparable durations, both by annual questionnaires (until September 1989), and by Central Registrar's Office records that provide the dates and certified causes of any deaths. Follow-up for death is continuing through these records, but in the analyses it was censored on 30 September 1990 to allow for delay in notification.

Statistical methods

These are as described in the Report to the MRC Leukaemia Committee on the Design and Analysis of Randomised Trials (Peto *et al.*, 1977), using "log rank" χ^2 and *P* values to test the statistical significance of any apparent differences in outcome, and "life-table" graphs to illustrate any such differences.

Results

There was no statistically significant difference between the 3 treatment groups in overall survival (Fig. 1, Table 2) or in the need for further treatment (usually transurethral resection) for local progres-

Table 1 Number of Patients Studied according to Possible Prognostic Variables, Duration of Follow-up and Allocated Treatment Group

	Allocated treatment group		
	Radiotherapy	Orchiectomy	Combination
Total no. of patients	88	90	99
Age at randomisation (years)			
<65	15	18	20
65-74	54	53	50
75+	19	19	29
T category			
T2	39	35	45
T3	35	36	37
T4	7	13	8
Not known	7	6	9
Gleason score			
Low (4-6)	24	20	24
Medium (7)	19	30	26
High (8-10)	29	25	40
Not known	16	15	9
Performance status			
Fully active	71	70	74
Restricted activity	11	11	15
Not known	6	9	10
Follow-up*			
Disease progression			
Median/maximum years	4.1/8.3	4.0/8.3	4.5/8.7
Death			
Median/maximum years	4.3/9.8	4.6/10.2	5.2/10.2

* Follow-up for local and distant disease progression was concluded on 30.9.89, follow-up for death was censored on 30.9.90, but is continuing through Central Registrar's Office records

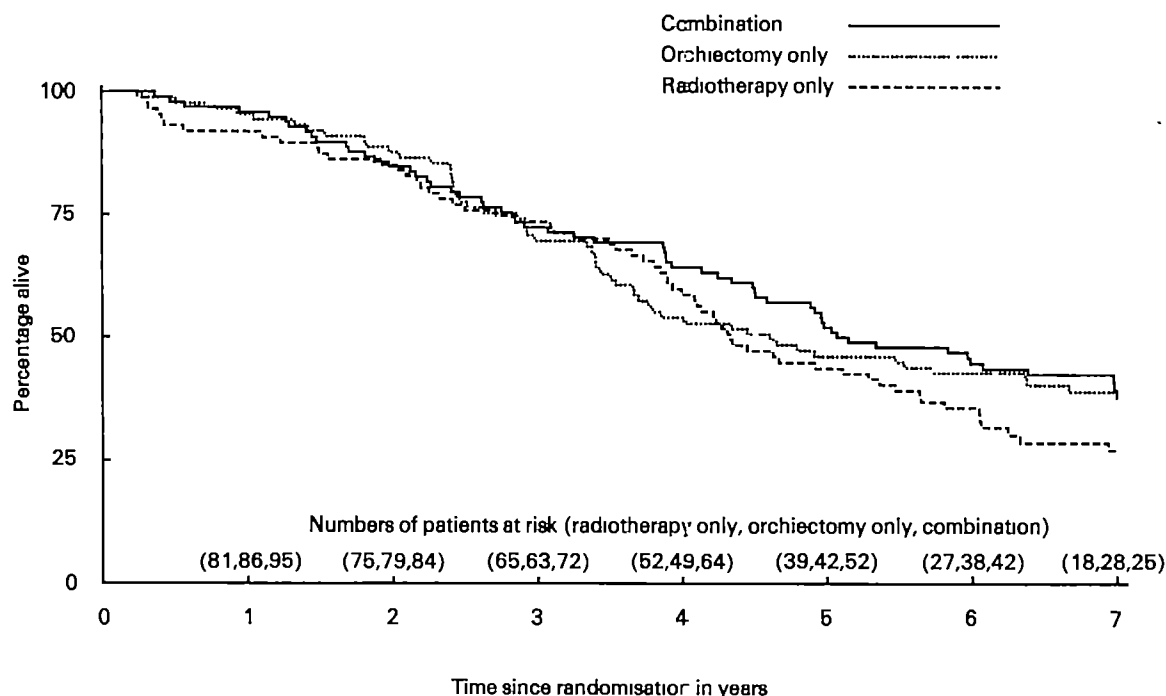


Fig. 1 Overall (all cause) mortality.

sion (Fig. 2, Table 2). However, the incidence of distant metastases was significantly ($\chi^2_2=13.27$, $2P<0.005$) higher in the group receiving radiotherapy alone than in either of the 2 groups that had orchiectomy (Fig. 3, Table 2).

Taking all 3 treatment groups together, the time to onset of metastases was not statistically signifi-

cantly related to age at randomisation ($\chi^2_2=1.83$). Metastases were, however, less frequent in patients with category T2 tumours ($\chi^2_3=12.27$, $2P<0.01$) or with low Gleason score ($\chi^2_3=14.18$, $2P<0.005$) and more frequent in patients with restricted activity ($\chi^2_2=6.41$, $2P<0.05$).

After stratifying for stage of tumour, Gleason

Table 2 Observed (O) and Expected (E) Number of Patients Dying, or Requiring Further Treatment for Local Progression, or Developing Distant Metastases, according to Initially Allocated Treatment

Allocated treatment group (no. of patients*)	Death from any cause†			Local progression needing treatment‡			Distant metastases**		
	O	E	O/E	O	E	O/E	O	E	O/E
Radiotherapy (88)	67	56.47	1.19	65	53.83	1.21	71	49.26	1.44
Orchiectomy (90)	58	61.73	0.94	55	58.23	0.94	55	63.78	0.86
Combination (99)	64	70.80	0.90	58	65.94	0.88	59	71.96	0.82
Total (277)	189	189.00	1.00	178	178.00	1.00	185	185.00	1.00

* 6 patients had no follow-up information on local progression (1 radiotherapy, 3 orchiectomy, 2 combination), 3 patients had no follow-up information on distant metastases (2 orchiectomy, 1 combination).

Logrank test for difference between the 3 treatment groups:

† $\chi^2_2=2.86$, not statistically significant.

‡ $\chi^2_2=3.46$, not statistically significant.

** $\chi^2_2=13.27$, $2P<0.005$.

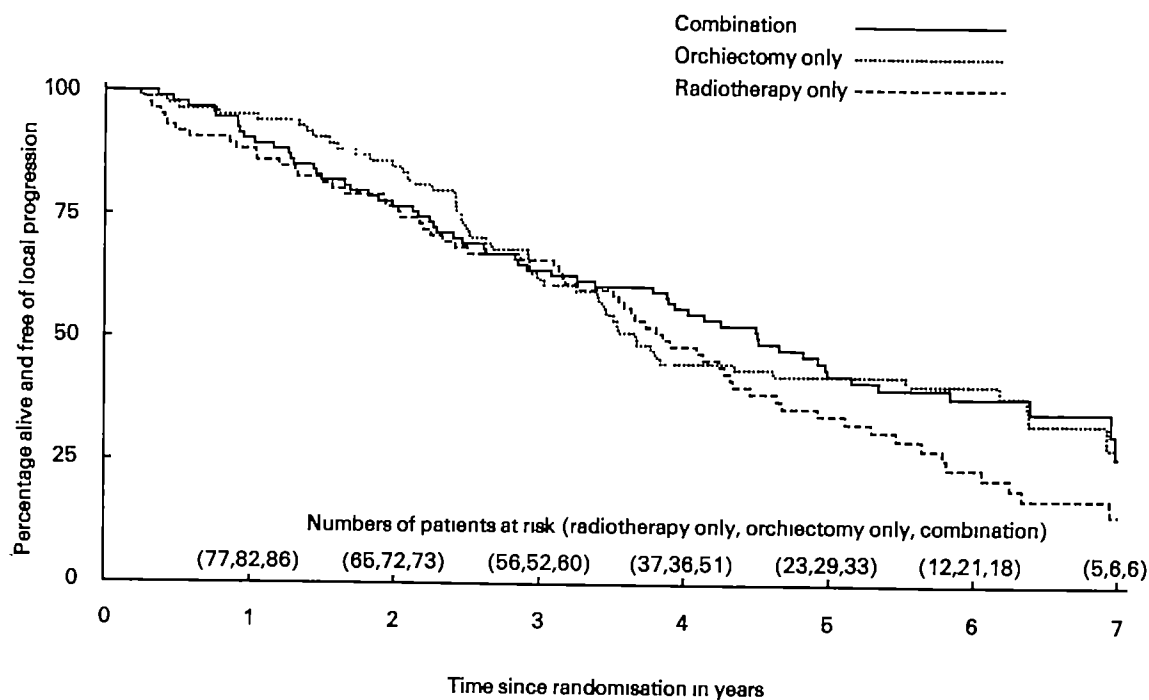


Fig. 2 Local progression needing treatment after trial entry

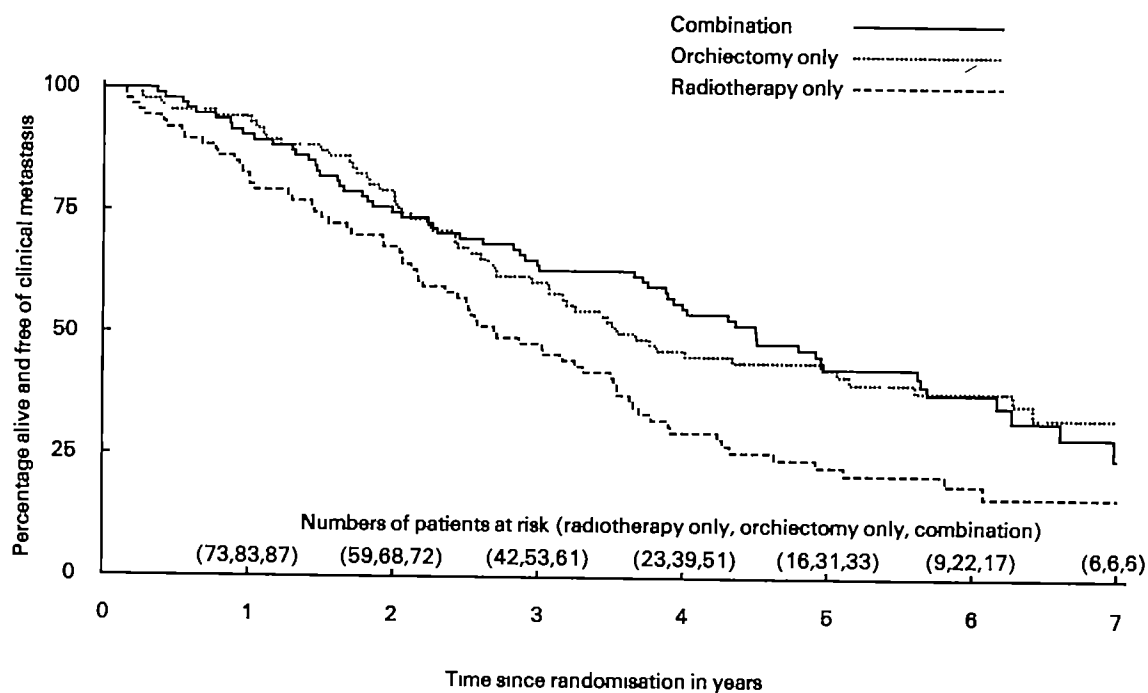


Fig. 3 Detection of metastases

score and performance status, the difference in the incidence of distant metastases remained statistically significant ($\chi^2_2 = 13.52$, $2P < 0.005$).

Of the 31 patients with adverse reactions attributed to orchiectomy (an incidence of 16%), 28 had troublesome hot flushes. It is doubtful whether the other 3 "adverse reactions" attributed to orchiectomy were in fact a result of the orchiectomy. They were rectal bleeding in a patient who did not have radiotherapy, frequency and urgency of micturition. Adverse reactions were attributed to radiotherapy in 48 patients (26%). Thirty-five had bowel symptoms and 15 had urinary symptoms other than transient frequency. Two patients had both bowel and urinary complications. Four had severe rectal bleeding necessitating transfusion. There was no case of bowel perforation or obstruction attributed to radiotherapy. Two patients who died had "radiation proctitis" recorded as a contributory cause of death, one of whom underwent an abdominoperineal excision of rectum for haemorrhage. No comparison of impotence in the different groups was possible as erectile impotence was known to be an almost inevitable direct effect of orchiectomy and was therefore rarely reported as a "side" effect.

Discussion

The major finding of the present study is that the incidence of distant metastases is higher in patients allocated to radiotherapy alone than in those allocated to orchiectomy either alone or combined with radiotherapy. It is probable that orchiectomy delays the appearance of metastases which were already present as undetectable micro-metastases when the patients first presented.

Patients whose disease progressed after radiotherapy usually then received hormone treatment. Perhaps because of this, there was no statistically significant difference in mortality between the 3 groups, but the numbers are not large enough to exclude any difference reliably. Radiotherapy and orchiectomy controlled local disease (as determined by the repeat transurethral resection rate) to a similar extent, and there was no evidence of additional benefit conferred by combined treatment.

Adverse reactions to radiotherapy are usually mild but are occasionally severe enough to be life-threatening (Sagerman *et al.*, 1989). The chief adverse effects of orchiectomy are impotence (which might not occur in patients treated just with radiotherapy) and hot flushes which, in some

patients, are severe. If orchiectomy, or some other hormonal treatment, is to be one of the main treatments of localised prostate cancer then it could generally be given either at about the time of diagnosis or later (perhaps some years later), when clear evidence of disease progression emerges. These alternative strategies are being compared in the current MRC trial of immediate versus deferred hormonal treatment.

It was concluded that orchiectomy delayed the onset of distant metastases, but in this study radiotherapy did not further delay metastases. Orchiectomy or radiotherapy, either alone or in combination, proved equally effective in controlling local disease during median follow-up periods of 4 to 4.5 years.

Acknowledgements

Acknowledgements are due to the following: Contributors—R S Adib, J. P. Blandy, C. A. C. Charlton, G. D. Chisholm, P. B. Clark, H. R. England, C. M. Evans, G. J. Fellows, J. A. Fleming, R. W. Glashan, P. A. Hamilton-Stewart, N. W. Harrison, W. F. Hendry, R. M. Jameson, Group Captain Jones, D. Mee, D. W. W. Newling, A. M. Paris, W. B. Peeling, B. Richards, M. R. Robinson, M. B. Rose, I. Smith, J. C. Smith, P. H. Smith, M. E. Snell, J. H. Steyn, K. C. Vaughton, H. N. Whitfield, J. E. A. Wickham, R. E. Williams, R. Witherow.

Other current and past members of the Medical Research Council Urological Cancer Working Party—Subgroup on Prostatic Cancer: M. R. Alderson, N. M. Bleehen, H. J. G. Bloom, F. J. Bramble, E. Charlton Edwards, C. D. Collins, H. Cuckle, P. Dawson-Edwards, T. J. Deeley, P. T. Doyle, W. Duncan, J. T. Flynn, J. C. Gingell, R. Gray, R. R. Hall, M. Harrison, D. Kirk, L. E. F. Moffat, W. J. Modle, A. R. Mundy, R. C. E. Pugh, W. M. Ross, L. G. Rowland, R. Scott, R. J. Shearer, P. J. B. Smith, B. A. De Sousa, D. A. Tolley, J. Webb, J. A. K. Wightman, G. Williams, J. L. Williams, C. Woodhouse.

Thanks are due to the radiotherapists who treated patients in this study, to Mrs Eileen Thompson for her assistance with data management, and to Mrs Pam Cain and Mrs Phyl Cosson-Molyneux for secretarial work.

References

- Hanks, G. E. (1989). External beam radiation therapy for prostate cancer clinically confined to the gland. *Urology (Suppl. 5)*, 33, 21–26.
- Lepor, H. and Walsh, P. C. (1988). Long term results of radical prostatectomy in clinically localised prostate cancer: experience at the Johns Hopkins Hospital. *Natl. Cancer Inst. Monogr.* 7, 117–122.
- Peto, R., Pike, M. C., Armitage, P. *et al.* (1977). Design and analysis of randomised clinical trials requiring prolonged observation of each patient. Part II: Analysis. *Br. J. Cancer*, 35, 1–39.
- Sagerman, R. H., Chun, H. C., King, G. A. *et al.* (1989). External beam radiotherapy for carcinoma of the prostate. *Cancer*, 63, 2468–2474.

Schröder, F. H. (1990) What is new in endocrine therapy of prostatic cancer? *EORTC Genitourinary Group Monograph 7 Prostate Cancer and Testicular Cancer*, ed. Newling, D. W. W. and Jones, W. G. Pp 45–52 New York: Wiley-Liss

The Authors

G. J. Fellows, MS, FRCS, Consultant Urologist, Churchill Hospital, Oxford.

P. B. Clark, MS, FRCS, Consultant Urologist, Leeds General Infirmary

L. L. Beynon, FRCS, Consultant Urologist, New Cross Hospital, Wolverhampton

J. Boreham, PhD, Research Officer, Radcliffe Infirmary, Oxford.
C. Keen, BS, FRCP, Consultant Radiotherapist, Mid-Kent Oncology Centre

M. C. Parkinson, BS, MRCS, FRCPath, Consultant Pathologist, Middlesex Hospital, London.

R. Peto, FRS, ICRF Reader in Cancer Studies, Radcliffe Infirmary, Oxford.

J. N. Webb, FRCP, Consultant Pathologist, Western General Hospital, Edinburgh.

Requests for reprints to: **G. J. Fellows**, Department of Urology, Churchill Hospital, Old Road, Headington, Oxford OX3 7LJ.

Prostate Cancer—the Impact of Irradiation on Urinary Outlet Obstruction

N. GREEN, D. TREIBLE, H. WALLACK and H. S. FREY

Division of Radiation Therapy and Division of Urology, Valley Presbyterian Hospital; Division of Urology, Los Robles Hospital, Van Nuys, USA

Summary—A series of 245 patients with prostate cancer treated by external irradiation was analysed to assess the impact of irradiation on urinary outlet obstruction. Prior to irradiation, obstruction was observed in 147/245 patients (60%). Irradiation either with or without hormonal therapy was as efficacious as transurethral resection of the prostate (TURP) in alleviating obstructive symptoms; 14/16 patients treated by irradiation alone responded, as did 19/19 who received hormonal therapy and irradiation and 109/112 who underwent TURP and irradiation. Following irradiation, 41/245 patients developed post-irradiation obstruction, 26/213 had post-irradiation strictures and 15/32 developed recurrent cancer. Surgical intervention was required less often for the management of recurrent obstruction caused by stricture as compared with recurrent cancer. TURP and urinary outlet obstruction acted as independent and additive variables to the development of post-irradiation stricture. Thus the avoidance of TURP in patients with obstructive symptoms reduced but did not eliminate the risk of developing a stricture.

Urinary outlet obstruction is a common complaint of patients with prostate cancer (Daponte *et al.*, 1983) and is often managed by TURP. However, if the patient then receives irradiation, TURP may predispose to the development of post-irradiation stricture (Seymore *et al.*, 1986). We evaluated patients treated by irradiation alone, hormonal therapy and irradiation, or TURP and irradiation. The obstructive symptoms were almost uniformly alleviated by each of these approaches. The avoidance of TURP in patients with obstructive symptoms reduced but did not eliminate the risk of post-irradiation stricture. Post-irradiation obstruction from urethral stricture could usually be managed by dilatation. Post-irradiation obstruction from recurrent cancer was uncommon and usually required surgical intervention.

Patients and Methods

Between October 1975 and October 1987, 321 patients were referred for definitive or adjunctive

irradiation; 26 patients who received ^{125}I and 40 who received adjunctive irradiation were excluded from the study. A total of 245 patients received definitive external beam irradiation and formed the basis of this study. The age range was 45 to 89 years (median 69). Patients were staged according to the extent of tumour spread as judged by rectal examination, operative findings, blood acid phosphatase, isotope bone scans, CT scans or bipedal lymphangiography; 21 patients had a staging laparotomy. A total of 23 patients had stage AII tumours; there were 37 BI, 38 BII, 96 CI and 51 CII lesions (Parry, 1989). Stage C was arbitrarily stratified to the classification of CI and CII. Stage CII was defined as a bulky prostate tumour with a minimum diameter of 6 cm and extension into the bladder or fixation to the pelvic side wall. Histopathology was categorised as low grade in 63 patients, intermediate in 101 and high in 81.

The diagnosis of urinary outlet obstruction was made from the patient's history, medical records and inquiry by the urologist. The diagnosis was based on the symptom complex of diminished calibre and force of the urinary stream, hesitancy

in initiating voiding and a sense of incomplete emptying of the bladder. A total of 105 patients had needle biopsy and 140 a TURP. Symptoms of urinary outlet obstruction were observed in 35 who had a needle biopsy and 112 who had a TURP. Routine cystoscopy was not done in patients who had a needle biopsy. Urological judgment determined which patients with obstructive symptoms received a TURP; 28 had a TURP only for tissue diagnosis. Of the 35 patients with obstructive symptoms who had only a needle biopsy, 16 were judged by the urologist to have mild obstruction and were treated by irradiation alone; 19 were judged to have more severe obstruction and were treated by hormonal therapy for 6 to 8 weeks prior to irradiation and while undergoing irradiation. Hormonal therapy was discontinued following irradiation. No uniform urological criteria were used to assign patients to the categories of mild or severe obstruction and the decision was based on urological judgment.

Irradiation was delivered with 4 MeV, 6 MeV or 18 MeV linear accelerator using opposing anterior and posterior portals to the entire pelvis and arc or rotation therapy to the prostate, 160 to 180 cGy per day, 5 days a week, for a total dose of 4500 to 4800 cGy delivered to the pelvis and 6500 cGy to the prostate. Following irradiation, the response of the primary tumour was recorded at intervals of 6 months to 1 year. Local control was recorded if the

prostate reverted to normal size and consistency or was no longer palpable. Routine post-irradiation biopsies were not done. Local failure was recorded if there was a persistent or recurrent area of induration. Follow-up ranged from 2 to 12 years (median 3). In all, 135 patients were followed up for 3 years, 95 for 4 to 10 years and 15 for 11 to 12 years. Following irradiation, persistent and recurrent urinary outlet obstruction was evaluated by the urologist, who determined it to be caused by urethral stricture or recurrent cancer.

Results

Urinary outlet obstruction was observed in 147/245 patients (60%) as the initial complaint. There was a trend towards increased frequency of urinary outlet obstruction with advancing stage: 20/23 patients (87%) AII, 16/37 (43%) BI, 11/36 (29%) BII, 57/96 (59%) CI and 36/51 (70%) CII; 35/147 patients (24%) with urinary outlet obstruction had a needle biopsy. A diagnostic TURP was performed in 28/98 patients (29%) who did not have obstructive symptoms (Table 1). Following irradiation, obstructive symptoms were alleviated in 14/16 patients treated by irradiation alone, in 19/19 treated by hormonal therapy and irradiation and in 109/112 treated by TURP and irradiation; 16/19 patients with more severe obstructive symptoms responded to hormonal therapy administered prior to radiation therapy. While undergoing irradiation, 6/16 patients with mild obstructive symptoms and 3/19 with more severe obstructive symptoms developed a transient increase in obstructive symptoms.

Local control was achieved in 213/245 patients (87%). Recurrent urinary outlet obstruction was observed in 41/245 cases (17%); in 26/213 (12%) this was due to post-irradiation stricture and in 15/32 (47%) to recurrent cancer (Table 2). Post-irradiation stricture occurred in 4/92 patients (4%)

Table 1 Relationship of Diagnostic Surgery to Urinary Outlet Obstruction

Obstruction prior to irradiation	Diagnostic surgery	
	TURP (%)	Needle biopsy (%)
Yes (n=147)	112/147 (76)	35/147 (24)
No (n=98)	28/98 (29)	70/98 (71)

Table 2 Urinary Obstruction

Surgical procedure	Onset		
	Before surgery (%)	After surgery (%)	After irradiation (%)
Needle biopsy	35/105 (33)*	35/105 (33)	11/105 (10.5)†
TURP	112/140 (86)	6/140 (5)	30/140 (21)††

* Urinary obstruction/total.

† 4 urethral strictures, 7 tumour recurrences.

†† 22 urethral strictures; 8 tumour recurrences.

in the needle biopsy group and 22/121 (18%) in the TURP group. There was a trend towards increased frequency of post-irradiation stricture according to advancing clinical stage; 4/23 (17%) AII, 3/36 (8%) BI, 3/33 (9%) BII, 10/86 (12%) CI and 6/35 (17%) CII. However, the clinical stage was not a significant factor as strictures did not occur in 62 patients in the needle biopsy group who did not present with obstructive symptoms. This included 19 BI, 14 BII, 23 CI and 6 CII. The presence of urinary outlet obstructive symptoms prior to irradiation and the performance of a TURP were found to be independent predisposing variables to the development of post-irradiation stricture. Thirty patients in the needle biopsy group who presented with obstructive symptoms were locally controlled; 2/16 treated by irradiation alone and 2/14 treated by hormonal therapy and irradiation developed post-irradiation stricture. Post-irradiation stricture also occurred in 2/23 patients who did not have obstructive symptoms prior to irradiation and had a TURP and in 20/98 (20%) who presented with obstructive symptoms and had a TURP.

Urological management of post-irradiation obstruction included urethral dilatation, TURP, suprapubic drainage and hormonal therapy. Invasive surgery was used more often to alleviate obstruction caused by recurrent cancer (Table 3).

Discussion

Urinary outlet obstruction is a common complaint of patients with prostate cancer (Daponte *et al.*, 1983) and 60% of our patients presented with obstructive symptoms. Urologists have favoured alleviating urinary outlet obstruction prior to irradiation, as there has been concern that the obstruction might get worse after the initiation of irradiation. If so, TURP might become necessary while the patient is undergoing irradiation and this could increase the risk of post-irradiation complications. Also, by delaying the scheduled delivery of irradiation, tumour control may be compromised (Perez *et al.*, 1986; Seymore *et al.*, 1986). There

have been no subjective or urodynamic criteria to determine which patient would develop increased urinary outlet obstruction following irradiation. Approximately 25% of our patients with obstructive symptoms were treated by irradiation alone or hormonal therapy prior to and concurrent with irradiation. The decision on treatment was based on urological judgment. If the urologist believed the obstruction was relatively mild, the recommendation was to use irradiation alone. If the obstruction was judged more severe, hormonal therapy was employed prior to irradiation. TURP was not recommended in those few patients who proved to be refractory to hormonal therapy. Although some patients did develop a modest increase in obstructive symptoms while undergoing irradiation, the symptoms were self-limiting. None developed total obstruction and none required either TURP or catheter drainage.

In our experience, irradiation alone or with hormonal therapy was almost uniformly effective in alleviating urinary outlet obstruction. A favourable response was probably due to the effects of irradiation on benign prostatic hypertrophy as well as cancer. Prostate cancer is often accompanied by benign prostatic hypertrophy (Greene, 1986; Walsh, 1986). In patients with small tumours it was difficult, if not impossible, to assign the obstruction to cancer alone. Following irradiation, the prostate usually reverted to normal size and consistency or was no longer palpable. These changes were indicative of the effects of irradiation on the non-malignant tissue as well as on the cancer.

Over 80% of our patients were locally controlled; 12% developed post-irradiation stricture. The true frequency may be underestimated, since the onset of urethral stricture was observed 1 to 6 years following irradiation and our median follow-up was 3 years. Obstructive symptoms and TURP were found to be independent predisposing variables. There was no significant correlation with stage classification. Urethral stricture can occur from TURP alone (Hart and Fowler, 1981). The surgical trauma of TURP and injury from irradiation

Table 3 Management of Post-irradiation Obstruction

	No treatment (%)	Urethral dilatation (%)	TURP (%)	Suprapubic drainage (%)	Hormonal therapy (%)
Stricture (n = 26)	2/26 (7)	16/26 (62)	6/26 (23)	0/26 (0)	0/26 (0)
Recurrent cancer (n = 15)	1/15 (7)	0/15 (0)	8/15 (53)	3/15 (20)	3/15 (20)

probably had an additive effect, resulting in a higher incidence of stricture with the use of both modalities as compared with either modality alone. Although uncommon, urethral stricture also occurred following the use of irradiation alone, especially in patients who presented with obstructive symptoms. The pathophysiological changes in the urethra that occur with obstruction may predispose to the development of post-irradiation stricture. The incidence of post-irradiation stricture was highest in patients who presented with obstructive symptoms and had a TURP, as compared with patients who had only 1 of these 2 variables. The incidence of post-irradiation obstruction was high in patients who had recurrent cancer. The management was more difficult. Post-irradiation stricture required either no therapy or was effectively managed by urethral dilatation. Obstruction caused by recurrent cancer usually required TURP or suprapubic cystoscopy.

This study has provided insight into measures that could be used to reduce the incidence of post-irradiation stricture. The most important measure is to be very selective in the use of TURP. Its avoidance may also improve disease-free survival. It has been alleged that TURP may increase dissemination of prostate cancer cells (Meacham *et al.*, 1989; Hanks, 1990). The option to avoid TURP was easy to exert in patients who had a TURP solely for tissue diagnosis. A needle biopsy is a reasonable alternative. One could also avoid TURP in patients who present with obstructive symptoms, since these can be alleviated by irradiation alone, hormonal therapy and irradiation, or a combination of both modalities (Fleischmann and Catalona, 1985; Perez *et al.*, 1986). The use of hormonal therapy with irradiation may decrease the incidence of post-irradiation obstruction from recurrent cancer, as the concurrent use of both modalities has been shown to improve tumour control and survival (Green *et al.*, 1984; Zagers *et al.*, 1988).

Acknowledgements

We thank our medical colleagues who helped with the preparation of this report and we thank Carol Gowdy for typing the manuscript.

References

- Daponte, D., Robinson, M. R. G. and Smith, P. H. (1983). Prognostic significance of the symptoms associated with prostatic carcinoma *Eur Urol*, **9**, 227-272.
- Fleischmann, J. D. and Catalona, W. J. (1985). Endocrine therapy for bladder outlet obstruction from carcinoma of the prostate *J. Urol*, **134**, 498-500.
- Green, N., Bodner, H. and Broth, E. (1984). Improved control of bulky prostate carcinoma with sequential estrogen and radiation therapy *Int J Radiat Oncol Biol. Phys.*, **10**, 971-976.
- Greene, L. F. (1986) Transurethral surgery In *Campbell's Urology*, ed. Walsh, P. C., Gittes, R. F., Perlmutter, A. D. and Stamey, T. A. Fifth edition. Volume III. Chapter 78, pp. 2815-2845. Philadelphia: Saunders.
- Hanks, G. E. (1990) The risk of distant metastases after transurethral resection of the prostate versus needle biopsy in patients with localized prostate cancer. *J. Urol.*, **144**, 751-752.
- Hart, A. J. L. and Fowler, J. W. (1981). Incidence of urethral stricture after transurethral resection of prostate *Urology*, **18**, 558-588-591.
- Meacham, R. B., Scardino, P. T. and Hoffman, G. S. (1989). The risk of distant metastases after transurethral resection of the prostate versus needle biopsy in patients with localized prostate cancer. *J. Urol.*, **142**, 320-375.
- Parry, W. L. (1989). Radical perineal prostatectomy In *Urologic Surgery*, ed Glenn, J. R. Third edition Chapter 93, pp. 957-959. Philadelphia: Lippincott.
- Perez, C. A., Philepich, M. V. and Zivanska, F. (1986) Tumor control in definitive irradiation of localized carcinoma of the prostate. *Int J. Radiat. Oncol. Biol. Phys.*, **12**, 523-531.
- Seymore, C. H., El-Mahdi, A. M. and Schellhammer, P. F. (1986). The effect of prior transurethral resection of the prostate on post-radiation urethral strictures and bladder neck contractions. *Int. J. Radiat. Oncol. Biol. Phys.*, **12**, 1597-1600.
- Walsh, P. C. (1986) Benign prostate hyperplasia. In *Campbell's Urology*, ed Walsh, P. C., Gittes, R. F., Perlmutter, A. D. and Stamey, T. A. Fifth edition. Volume II. Chapter 27, pp. 1248-1265. Philadelphia: Saunders.
- Zagers, G. K., Johnson, D. E. and von Eschenbach, A. C. (1988). Adjuvant estrogen following radiation therapy for stage C adenocarcinoma of the prostate: long-term results of a prospective randomized study *Int. J. Radiat. Oncol. Biol. Phys.*, **14**, 1085-1091.

The Authors

- N Green, MD, FACR, Director, Division of Radiation Therapy, Clinical Professor, LAC/USC Medical Center.
- D Treible, MD, Clinical Instructor, Loma Linda University.
- H Wallack, MD, Urologist, Los Robles Hospital
- H S. Frey, MD, PhD, Clinical Associate Professor, University of California, Los Angeles

Requests for reprints to N Green, Division of Radiation Therapy, Valley Presbyterian Hospital, 15107 Vanowen Street, Van Nuys, California 91405, USA

Screening for Bacteriuria in Urological Patients using Reagent Strips

SARAH J. MILLS, M. FORD, F. KATE GOULD, SALLY BURTON and D. E. NEAL

Departments of Urology and Microbiology, Freeman Hospital, Newcastle upon Tyne and Department of Surgery, University of Newcastle upon Tyne

Summary—A rapid and accurate ward-based method of diagnosing urinary infection would be of value in determining the prescription of antibiotics in pre-operative urological patients. This study describes the sensitivity and specificity of a screening technique based on commercially available reagent strips in the diagnosis of urinary infection. A total of 222 pre-operative samples and 83 post-operative samples was studied to compare the results of formal urine culture and reagent strips.

Using a definition of a positive nitrite or a positive leucocyte esterase on the reagent strips as being suggestive of infection, it was found that the strips had a sensitivity of 91% and a specificity of 85% compared with formal culture in pre-operative samples. The results from post-operative samples were less satisfactory, the strips having a sensitivity of only 71% and specificity of 55%. The strips were insensitive but specific in the identification of pyuria in pre-operative specimens.

These results suggest that reagent strips can be used as a ward-based method to identify men at risk of infection before urological procedures, and may allow selectivity in the use of peri-operative antibiotics.

Bacteraemia is found in 60% of men undergoing transurethral prostatectomy who have bacteriuria or indwelling urethral catheters before operation, and septicaemia occurs in 6% of this group: these data argue strongly in favour of the use of peri-operative antibiotics in such patients. In men with sterile urine, the incidence of septicaemia and bacteraemia is much lower, being about 1% and 25% respectively (Grabe, 1987), although even in those with sterile urine, bacteria are present in the prostates of 25% (Gorelic *et al.*, 1988). There is also good evidence that the morbidity of instrumentation of the urinary tract is significantly increased in the presence of infected urine (Sullivan *et al.*, 1973; Quintiliani *et al.*, 1978) and that the morbidity of prostatectomy can be decreased in such circumstances by the administration of peri-operative antibiotics (McEntee *et al.*, 1987). On the other hand, evidence that the use of peri-operative parenteral

antibiotics can reduce morbidity in men with sterile urine or those without indwelling urethral catheters before operation remains uncertain (Grabe, 1987). Another period of high risk for men undergoing prostatectomy is the time of catheter removal (Gordon *et al.*, 1983), when there is a case to be made for the routine administration of a short course of oral antibiotics to men at high risk—*e.g.* those with pre-operative infection, those with long-term indwelling catheters and those likely to experience difficulty in achieving complete bladder emptying after prostatectomy, such as men with chronic retention.

Many urologists, therefore, operate a selective policy for the administration of peri-operative antibiotics. Crucial to the success of such a policy is the prompt identification of those with pre-operative bacteriuria; herein lies a number of potential difficulties. The results of formal urine culture take 24 h to obtain, and therefore several screening methods have been introduced (Stevens, 1989). One commonly used method involves the use

of a particle counter which permits identification of bacteriuria with a good degree of sensitivity. Unfortunately, urine samples suspected to be positive by this technique will then require formal culture for confirmation.

A ward-based method of identifying patients with bacteriuria quickly and reliably would be beneficial. It is important for such tests to have high sensitivity and also desirable for them to be specific, to reduce costs and to diminish the risk of the emergence of resistant organisms which might occur with unnecessary antibiotic administration. The use of reagent strips which detect blood, leucocyte esterase and nitrites has been reported to be useful in the diagnosis of urinary infection in an elderly population (Flanagan, 1989). We have evaluated the use of such strips in a urological population.

Materials and Methods

We evaluated a total of 305 urine samples from 222 men (mean age 65 years, range 16–96) admitted to 1 urological ward between September 1990 and February 1991: these samples were obtained from 222 men studied before operation and 83 of them afterwards. In all, 32 men had indwelling catheters at the time of admission. Of these, 60% were admitted for endoscopic procedures and 15% for open surgery; the remainder were emergency admissions or undergoing urological investigation.

Mid-stream or catheter urine samples were taken on admission, whereas specimens after operation were all taken from the catheters of men undergoing endoscopic procedures. Specimens were collected in the morning by the nursing staff and transported promptly to the laboratory for culture. All specimens were tested with reagent strips immediately after collection and the results read and recorded by the nursing staff. The strips used were the Ames Multiple Reagent Strips (Ames Division, Miles Laboratory Ltd). These are firm plastic strips with reagent areas for glucose, bilirubin, ketone, specific gravity, blood, protein, nitrite and leucocyte esterase. We limited our observations to results for blood, protein, nitrite and leucocyte esterase, recording any reaction greater than trace positive as representing a positive result. The nitrite test depends upon the conversion of nitrate to nitrite, which is principally a feature of gram-negative bacteria. The test is specific for nitrite and if positive suggests the presence of $>100,000$ organisms/ml. False negative results can occur when urinary tract infections are caused by organisms

that do not contain nitrate reductase, when urine has been in the bladder for insufficiently long periods for the reduction of nitrate to occur (e.g. when indwelling catheters are present), or when dietary nitrate is absent. A positive leucocyte esterase test depends on the presence of esterase in granulocytic leucocytes. The sensitivity of this test can be affected by the presence of certain drugs in the urine.

Urine samples were cultured by the standard technique of our laboratory. Calibrated loops are used which deliver $1\mu\text{l}$ urine on to blood and MacConkey agar plates; these plates are incubated overnight at 37°C in air. Using the results of formal urine culture results as our gold standard, the sensitivity and specificity were calculated separately and in combination for each of the 4 reagent strip parameters mentioned above. A positive culture result was considered initially as $>100,000$ colony forming units per ml (cfu/ml) of a single organism. We also re-calculated the sensitivity and specificity of the strips after broadening the definition of infection to include results of formal cultures when $<100,000$ cfu of 2 different organisms were present. Contaminated specimens, where low counts of multiple organisms were present ($<20,000$ cfu/ml), were grouped with the negative cultures which were otherwise defined as containing $<20,000$ cfu/ml. Pre-operative and post-operative samples were analysed separately, and amongst the pre-operative samples we reported the results separately for those with or without indwelling catheters.

Results

Of the 222 pre-operative urine specimens 31 (14%) were infected, using a definition of $>100,000$ cfu/ml of a single organism; 7% were contaminated and 79% were sterile. When the definition of a positive culture included cultures of 2 organisms, 16% were infected, 5% were contaminated and 79% were sterile. The types of organisms cultured are reported in Table 1. Thirty-two of the 222 men had indwelling catheters and of these samples, 34% were infected, 25% were contaminated and 41% sterile.

The sensitivity and specificity calculated for each of the 4 parameters in the reagent strips in isolation are shown in Table 2 for the pre-operative urine specimens. When a positive reagent result was defined as being either nitrite positive or leucocyte esterase positive, sensitivity was 91% and specificity was 85%. Moreover, when men with indwelling

Table 1 Results of Formal Culture

<i>> 100,000 cfu/ml for single organisms</i>	
Coliforms*	15
<i>Pseudomonas</i>	5
<i>Klebsiella</i>	4
<i>Enterococcus faecalis</i>	3
Coagulase negative staphylococci	2
<i>Proteus</i>	1
<i>Staph aureus</i>	1
<i>> 100,000 cfu/ml for 2 organisms</i>	
<i>Pseudomonas</i> + <i>Enterococcus</i>	1
Coliform + <i>Candida</i>	1
Coliform + <i>Klebsiella</i>	1
<i>< 100,000 > 1000 cfu/ml</i>	
Diphtheroid†	1

* Coliform organisms were gram-negative, oxidase-negative, non-lactose fermenting bacilli.

† Probable contaminant.

Table 2 Pre-operative Urine Specimens: Reagent Strips Compared with Formal Urine Culture

	Sensitivity (%)	Specificity (%)
Nitrite	60.5	94.6
Protein	52.6	62.2
Leucocyte	78.9	87.0
Blood	65.8	71.9

catheters were excluded from these results the sensitivity was 89% and the specificity was 91%. When a positive formal urine culture was defined as $> 100,000$ cfu/ml of 1 or 2 organisms, the sensitivity was 88% and the specificity was 86%. The frequency distribution of bacterial concentrations in urine specimens which grew any organisms at all was as follows: 69% were infected with $> 100,000$ cfu/ml, 9% grew 2 different organisms at counts of $> 100,000$ cfu/ml; only 1.5% of specimens grew a single organism at concentrations between $> 20,000$ and $< 100,000$ cfu/ml: the remainder were contaminated with mixed growth of > 2 organisms at low counts.

After operation, 6% of patients who had sterile urine beforehand and who had undergone endoscopic procedures developed infected urine post-operatively. Of the 83 specimens studied after operation, 18% were infected, 7% were contaminated and 75% were sterile. None of the 4 reagent strip parameters enabled infection to be diagnosed in this group with good sensitivity and specificity. The best combination of parameters in the pre-operative specimens (nitrite positive or leucocyte

esterase positive) gave a sensitivity of 71% and a specificity of 55%.

Pyuria was present in 75 patients studied before operation and this was identified by a positive leucocyte esterase test in 47 of them (sensitivity = 63%); 10 of 142 patients had a false positive test (specificity = 93%).

Discussion

These results suggest that reagent strips have a good sensitivity and specificity in the diagnosis of urinary infection in pre-operative ward-based samples from men undergoing urological surgery. One problem in the evaluation of the reagent strips arose in deciding the best definition of urinary tract infection in the context of a cohort of urological patients. The conventional criteria are those of Kass (1957), who compared the sensitivity of mid-stream urine specimens with the culture of suprapubic specimens in the detection of *E. coli* infection. It should be noted that he found that more than 100,000 colony forming units (cfu/ml) of *E. coli* in 3 mid-stream specimens was highly significantly associated with the presence of *E. coli* in suprapubic specimens. In practice, this definition has been broadened to include other organisms and is often taken to include only 1 positive mid-stream specimen. Many studies of urinary infection and prostatectomy (Symes *et al.*, 1972; Jackaman and Chisholm, 1975; Houle *et al.* 1989) and the use of reagent strips (Bolann *et al.*, 1989; Flanagan *et al.*, 1989) have accepted this definition. However, some authors have suggested that lower concentrations of bacteria in mid-stream specimens may be significant and that low concentrations of bacteria from catheter specimens in the early post-operative period after prostatectomy may also be significant (Essenhigh and Clayton, 1970; Bruce *et al.*, 1971; Gorcon *et al.*, 1983). It has been advocated that the definition should be tailored to the population under analysis (Stevens, 1989) and furthermore, that a frequency distribution of bacterial counts be produced during evaluation of bacteriuria screening systems (Johnson *et al.*, 1982). In practice, we found that few specimens in our population of men grew organisms at concentrations between 20,000 cfu/ml and $> 100,000$ cfu/ml.

Pyuria was detected in only 63% of patients studied before operation in whom pyuria was detected by microscopy, although the reagent strips were accurate in identifying men without pyuria (specificity: 93%). This study was not designed to determine the use of the strips in detecting sterile

pyuria, but the results shown here do not suggest that a negative test could be used with confidence in the out-patient department to exclude sterile pyuria, although a positive test might be useful.

In calculating the ability of the reagent strips to detect bacteriuria, we initially looked at the results using a definition of $>100,000$ cfu/ml of a single organism and then included specimens with 2 different organisms at $>100,000$ cfu/ml, as these are unlikely to represent contamination. We found that it is possible to identify with accuracy significant bacteriuria in pre-operative specimens by the use of reagent strips. The clinical application of this would be the prescription of prophylactic antibiotic cover for the cohort undergoing endoscopic surgery. It is usual practice in this unit to give antibiotics to all patients with indwelling catheters on the assumption that they have an associated bacteriuria. Therefore, we calculated the sensitivity and specificity of the reagent strips after excluding this group. On this basis we detected 89% of patients with pre-operative bacteriuria. This, we feel, is good enough to indictate the prescribing of antibiotic prophylaxis. In addition, with a specificity of 91%, we would not be prescribing unnecessarily in many patients, with the attendant cost and danger of promoting bacterial resistance which that incurs. We feel that these reagent strips have a role to play in the examination of pre-operative specimens from male urological patients.

Acknowledgements

We thank the nursing staff of Ward 3, Freeman Hospital, who helped with the study, and Messrs D. M. Essenhigh and R. R. Hall, who allowed us to study their patients.

References

- Bolann, J., Sandberg, S. and Digraes, A. (1989). Implications of probability analysis for interpreting results of leucocyte esterase and nitrite test strips *Clin Chem.*, **35/8**, 1663-1668.
- Bruce, A. W., Rao, C. R. and Kennedy, W. (1971) Prostatectomy and infection. *J. Urol.*, **106**, 910-912.
- Essenhigh, D. M., Clayton, C. B. and Taha, M. A. (1970). The use of Lasix (frusemide) in the prevention of urinary infection following prostatectomy. *Br J Urol*, **42**, 450-456.
- Flanagan, P. G., Davies, E. A., Rooney, P. G. *et al.* (1989). Evaluation of four screening tests for bacteriuria in elderly people. *Lancet*, **i**, 1117-1118.
- Grabe, M. (1987). Antimicrobial agents in transurethral prostatic resections. *J. Urol.*, **138**, 245-252.
- Gordon, D. L., Bune, A., Grime, B. *et al.* (1983). Diagnostic criteria and natural history of catheter associated urinary tract infections after prostatectomy. *Lancet*, **ii**, 1269-1271.
- Gorelic, J. I., Senterfit, L. B. and Darracott Vaughan, E. (1988). Quantitative bacterial tissue cultures from 209 prostatectomy specimens. *J. Urol.*, **139**, 57-60.
- Houle, A. M., Mokheas, I., Sarto, N. *et al.* (1989). Perioperative antibiotic prophylaxis for transurethral resection of the prostate: is it justifiable? *J. Urol.*, **142**, 317-319.
- Jackaman, F. R. and Chisholm, G. D. (1975). Urinary infection and prostatectomy. *Br. J. Urol.*, **47**, 545-548.
- Johnson, H. H., Curtis, G. D. W. and Nichols, W. W. (1982) Current status of bioluminescence as a means of detecting significant bacteriuria. In *Rapid Methods and Automation in Microbiology*, ed. Tilton, R. C. Pp. 162-165 Washington American Society for Microbiology.
- Kass, E. H. (1957) Bacteriuria and the diagnosis of infections of the urinary tract. *Arch Intern Med.*, **100**, 709-714.
- McEatee, G. P., McPhail, S., Mulvin, D. *et al.* (1987). Single dose antibiotic prophylaxis in high risk patients undergoing transurethral prostatectomy. *Br. J. Surg.*, **74**, 192-194.
- Quintiliani, R., Klinek, J., Cunha, B. A. *et al.* (1978) Bacteraemia after manipulation of the urinary tract. The importance of pre-existing urinary tract disease and compromised host defences. *Postgrad Med J.*, **54**, 668-671.
- Stevens, M. (1989). Screening urines for bacteriuria. *Med Lab Sci.*, **46**, 194-206.
- Sullivan, N. M., Sutter, V. L., Nims, M. M. *et al.* (1973). Clinical aspects of bacteraemia after manipulation of the genito-urinary tract *J Infect. Dis.*, **127**, 49-55.
- Symes, J. M., Hardy, D. G., Sutherland, K. *et al.* (1972) Factors reducing the rate of infection after transurethral surgery. *Br. J. Urol*, **44**, 582-586.

The Authors

Sarah J. Mills, MB, BS, Registrar in Urology.
 M Ford, FIMLS, Senior Medical Laboratory Scientific Officer, Department of Microbiology.
 F. Kate Gould, MRCPATH, Consultant Microbiologist, Department of Pathology.
 Sally Burton, RGN, Nursing Sister, Department of Urology.
 D E Neal, MS, FRCS, BSc, Senior Lecturer and Honorary Consultant Urological Surgeon, Department of Urology and University Department of Surgery

Requests for reprints to: D E. Neal, Department of Urology, Freeman Hospital, Freeman Road, High Heaton, Newcastle upon Tyne NE7 7DN.

PAEDIATRIC UROLOGY

Clinicopathological Study of Nephroblastomas in Ibadan

E. E. U. AKANG, J. U. OKPALA, Y. ILIYASU and J.

Departments of Pathology, Paediatrics and Surgery, University College Hospital, Ibadan, Nigeria

Summary—The present study reviews 31 patients with histologically confirmed nephroblastoma seen over a 5-year period (1985–1989). There was a predominance of female patients with a male:female ratio of 1:1.7, and the average age of the patients was 47 months. The patients invariably presented with a palpable abdominal mass, but haematuria was exceptional. The neoplasms tended to be larger on average than those reported previously among Caucasian children. Carcinomatous transformation of the epithelial components was observed in 2 renal neoplasms. Poorly differentiated neoplasms were commoner in male than in female patients. Our findings indicate an unfavourable prognosis for nephroblastoma in this environment because of late clinical presentation with advanced disease and inadequate treatment and follow-up.

Nephroblastomas are malignant embryonal neoplasms of the kidney which are characterised by triphasic differentiation into epithelial, stromal and blastemal elements (Marsden and Steward, 1976; Beckwith, 1983; Variend *et al.*, 1984). Ultrastructural studies support the widely accepted belief that these neoplasms originate from the metanephric blastema (Williams and Ajayi, 1976).

The occurrence of nephroblastomas has previously been thought to be constant worldwide, with a uniform incidence of 10 cases per 1000 children (Seemayer and Cavenee, 1989). Recent reports, however, indicate a low incidence of Wilms' tumour in Japanese children (Miller, 1988).

The present study was undertaken to review the clinical and pathological features of nephroblastomas in Ibadan, Nigeria.

Patients and Methods

Thirty-one patients with histologically confirmed nephroblastoma were registered in the Ibadan Cancer Registry between 1985 and 1989. The clinical and surgical pathology data of these cases were obtained from the patients' case notes and the

records of the Department of Pathology, University College Hospital, Ibadan. The patients' histological slides were reviewed and the neoplasms classified according to the method of Stowens (1966).

Results

There were 12 male and 19 female patients, giving a male:female ratio of 1:1.7. The ages of 30 patients ranged from 6 months to 15 years (average age 47 months) and a peak incidence in the first quinquennium (0–4 years), as shown in the Figure. One patient was an adult male of unstated age.

The clinical signs and symptoms of 23 patients are shown in Table 1. The children invariably had a palpable abdominal mass, which was painful or tender in 6 cases. Weight loss and pyrexia were also relatively common findings. Unusual presenting features included pruritus, vomiting and cough. Only 1 patient had frank macroscopic haematuria.

Intravenous urography was diagnostic in the cases in which it was performed. The usual findings were an enlarged non-functioning kidney during the nephrogram phase, or distorted and displaced calices during the excretory phase. Ultrasonography was also helpful in confirming the presence of a soft tissue lumbar mass displacing the kidneys, and in the detection of liver metastases. In some

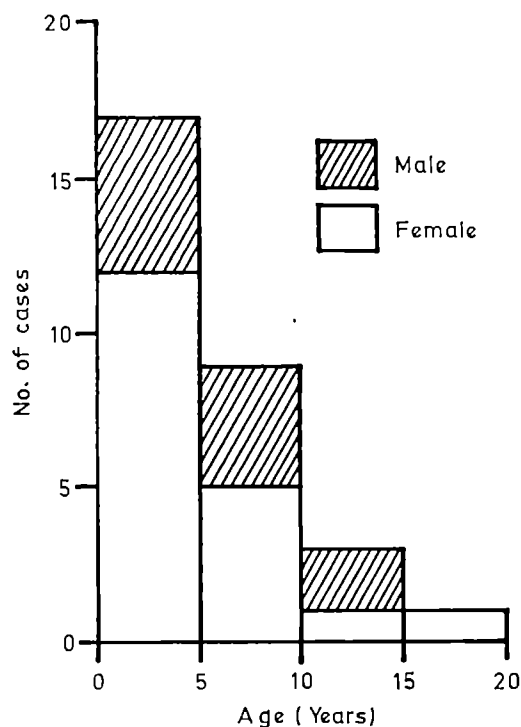


Fig. Age and sex distribution of patients with nephroblastoma.

cases chest X-ray demonstrated cannonball metastases.

Nineteen patients underwent nephrectomy. In 8 additional patients the tumour was too far advanced for resection and only a confirmatory tumour biopsy could be obtained.

The usual operative finding was of a huge, vascular, apparently encapsulated renal mass. In some cases the tumour was adherent to the liver or intestines. Three patients had para-aortic lymph

Table 1 Clinical Features

Clinical feature	No of patients	%
Abdominal mass	23	100
Weight loss	11	48
Fever	7	30
Abdominal pain	6	26
Vomiting	2	9
Pallor	2	9
Pruritus	2	9
Haematuria	1	4
Cough	1	4

node metastases and 3 had omental metastases, with inferior vena caval invasion in 2 cases. One patient had haemorrhagic ascites at laparotomy and a second patient had post-traumatic haemoperitoneum.

Post-operative combination chemotherapy with vincristine and actinomycin D, cyclophosphamide or cytosine arabinoside was administered in most cases, in combination with radiotherapy. A major problem was incomplete therapy due to loss of the patients to follow-up or inability of their parents to afford the cost of combination chemotherapy and radiotherapy. The post-operative duration of follow-up in 11 patients ranged from 2 to 16 months (mean 6.6).

The weights of the nephrectomy specimens ranged from 260 to 4800 g (mean 1170) and increased proportionally with increasing age. Similarly, the maximal diameters of the specimens ranged from 11 to 20 cm (mean 15) and also increased proportionally with age.

The cut surfaces of the neoplasms appeared fleshy grey or yellowish-pink with areas of haemorrhage, necrosis or cystic degeneration.

Microscopically, the neoplasms were composed of an admixture of epithelial, stromal and blastemal components, with 26 neoplasms (93%) containing all 3 and only 2 (7%) containing 2 elements (Table 2).

Table 2 Histological Features

<i>Differentiation</i>		
Epithelial	(27)	(96)
Glomeruli	17	61
Tubules	24	86
Stromal	(28)	(100)
Mesenchyme	20	71
Fibrocollagenous	21	75
Smooth muscle	13	46
Skeletal muscle	4	14
Cartilage	3	11
Bone	1	4
Fat	1	4
Blastemal	(27)	(96)
Oncocytoid metaplasia	2	7
Rosettes	1	4
Alveolar structures	2	7
<i>Tumour spread</i>		
Vascular	5	18
Hilar	6	21
Capsule	3	11
Liver	1	4
Lymphatic	2	7

Epithelial tubules were present in 24 neoplasms (86%) and the pathognomonic glomeruloid bodies were seen in 17 (61%). In 1 case each, either focal transitional cell carcinoma or basal cell carcinoma was identified in an otherwise typical nephroblastoma.

All 28 neoplasms histologically reviewed contained stromal elements. The commonest representatives were fibrous tissue or loose mesenchyme. Smooth muscle, skeletal muscle, cartilage, bone and fat were less frequently observed. Six neoplasms showed sarcomatous transformation of these stromal elements.

Blastemal elements of nephroblastomas were typically composed of sheets of small round cells with large nuclei and scanty cytoplasm separated into lobules by mesenchymal or fibrous septa. In 2 cases the blast cells showed abundant eosinophilic cytoplasm (oncocytoïd metaplasia). Tumour rosettes and alveolar structures were seen in 1 case each.

Two neoplasms containing many well formed glomeruloid bodies and tubular structures were classified as Class I nephroblastomas. In 10 additional cases there were fewer, less well differentiated glomeruloid or tubular structures (Class 2). In 7 cases there were scanty glomeruloid bodies, and poorly formed tubules lined by stratified epithelium (Class 3). Three Class 4 neoplasms were characterised by the absence of differentiated epithelial tubules or glomeruli. Four neoplasms were not classifiable into the above categories either because they were composite, in 2 cases (Class 6), or because the biopsy was too small for evaluation.

Class 3 and Class 4 neoplasms were more common in male patients than in female patients.

There was histological invasion of the hilar connective tissue in 6 cases, blood vessels in 5 cases and the renal capsule in 3 cases. The perirenal and peri-ureteric lymphatic vessels were infiltrated in 2 cases.

Incidental degenerative changes observed in some neoplasms included haemorrhage, necrosis and, rarely, dystrophic calcification. There was associated chronic pyelonephritis in 2 patients and obstructive uropathy in 3.

Discussion

There was a predominance of female patients in our study group. This contrasts with the earlier studies of Williams (1975) and Junaid and Babalola (1988) among Nigerian children as well as that of Olisa *et al.* (1975) among black American children,

where a slight male predominance was reported. However, an equal sex incidence has been observed by Davey (1964) also from Ibadan, Molyneux (1979) in Malawi, Hussain *et al.* (1988) in Sudan and among Caucasian children (Stowens, 1966; Marsden, 1976; Marsden and Steward, 1976).

The mean age of the children in this study was 47 months. This is twice as high as the average age of 23 months cited by Davey (1964) from this same environment. The majority of nephroblastomas arise before the age of 7 years (Williams, 1975; Marsden and Steward, 1976) but nephroblastomas are unusual before 3 months of age (Boland, 1971). They rarely arise in adult patients (Lurie *et al.*, 1988).

The patients in this study invariably presented with an abdominal mass, which was painful in about one-third of the cases. Other common clinical findings were weight loss and fever. Haematuria was exceptional and only occurred in a single patient. Our findings are again similar to those of Davey (1964) and Sinnette (1967) from this same environment, who both commented on the rarity of haematuria in patients with nephroblastoma. In contrast to our findings, Marsden and Steward (1976) observed that 15 (19%) of their 81 Caucasian children with nephroblastoma had haematuria. Haematuria was commoner in the early stages of presentation, since 6 of the 7 children in their series who had no clinically palpable mass had haematuria.

Another indicator of the late clinical presentation of African children with nephroblastoma is the massive enlargement of the renal mass, up to 4.8 kg in the present study and 5.664 kg in the study by Davey (1964). By contrast, the largest tumour reported by Marsden and Steward (1976) was 1.5 kg.

Our renal neoplasms showed characteristic triphasic differentiation, with the formation of well recognised histological patterns as previously described (Stowens, 1966; Marsden and Steward, 1976; Beckwith, 1983; Variend *et al.*, 1984). Male patients tended to have more poorly differentiated neoplasms than female patients. This might imply a poorer prognosis in males, since the degree of epithelial differentiation in nephroblastomas shows a positive correlation with prognosis (Benington and Beckwith, 1975; Boland, 1979; Lurie *et al.*, 1988). Unfortunately, most of our patients were lost to follow-up and are presumed to have died.

Apart from the occurrence of stromal sarcomatous transformation in 21% of our cases, a further 2% showed malignant epithelial components remi-

niscent of basal cell or transitional cell carcinoma. Anaplastic or sarcomatous stromal transformation in nephroblastomas is associated with an unfavourable prognosis (Beckwith, 1983; Lurie *et al.*, 1988).

Also of interest is the confirmation by our study of the observation by Davey (1964) that the frequency of nephroblastoma was identical to that of renal carcinoma. During the 5-year period covered by the study, there were 29 cases of renal carcinoma occurring in 11 male and 18 female patients. The ages of these patients ranged from 9 to 80 years (mean 43.3). Only one of these patients was aged less than 15 years.

Our findings contrast with the situation in Caucasian patients, where renal carcinoma outnumbered nephroblastoma. This indicates that the age population distribution of Nigerians may not have changed remarkably and life expectancy is still lower in this environment than among Caucasian patients. This hypothesis may be validated by the proposed national census due to take place in Nigeria in October 1991.

In conclusion, the present study suggests that nephroblastoma is still a significant cause of morbidity and mortality in children in Ibadan. Unfortunately, children with this neoplasm tend to present at a late stage with far advanced disease and only palliative therapeutic measures are instituted. However, the parents of afflicted children often cannot afford the cost of comprehensive multimodality therapy and the patients are often lost to follow-up. These poor results locally are in contrast to recent improvements in the prognosis of Wilms' tumour in Caucasian children with the introduction of intensive therapeutic regimens (Lurie *et al.*, 1988).

References

- Beckwith, J. B. (1983). Wilms' tumor and other renal tumors of childhood *Hum Pathol.*, **14**, 481-492.
- Bennington, J. L. and Beckwith, J. B. (1975) *Tumors of the Kidney, Renal Pelvis and Ureter Atlas of Tumor Pathology* Second Series. Fascicle 12 Pp. 31-91. Washington. Armed Forces Institute of Pathology.
- Bolande, R. P. (1971). Benignity of neonatal tumors and concept of cancer regression in early childhood *Am J. Dis. Child.*, **122**, 12-14.
- Bolande, R. P. (1979) Developmental pathology. *Am J. Pathol.*, **94**, 634-684.
- Davey, W. W. (1964) Renal tumours in Nigeria. *Br. J. Urol.*, **36**, 340-346.
- Hussain, M. A. M., Abbas, F. E. M. and Ahmed, H. M. (1988). Malignant disease in Sudanese children. *East. Afr. Med. J.*, **65**, 507-514.
- Junaid, T. A. and Babalola, B. O. (1988). The Ibadan Cancer Registry, 1960-1984. *I.A.R.C. Sci. Publ.*, **87**, 37-44.
- Lurie, M., Iannina, S., Mexz, Y. *et al.* (1988). Adult nephroblastoma. *Cancer*, **61**, 2342-2347.
- Marsden, H. B. (1976) Morphology and incidence of childhood tumours *J Clin Pathol.*, **29**, 1016-1021.
- Marsden, H. B. and Steward, J. K. (1976). Renal tumours. *Recent Results Cancer Res*, **13**, 327-361.
- Miller, R. W. (1988). Geographical and ethnic differences in the occurrence of childhood cancer. *I.A.R.C. Sci. Publ.*, **87**, 3-7.
- Molynaux, E. M. (1979). Childhood malignancies in Malawi 1967-76. *East Afr. Med. J.*, **56**, 15-25.
- Olisa, E. G., Chandra, R., Jackson, M. A. *et al.* (1975). Malignant tumors in American black and Nigerian children. a comparative study *J Natl Cancer Inst.*, **55**, 281-284.
- Seemayer, T. A. and Cavenee, N. K. (1989). Molecular mechanisms of oncogenesis. *Lab Invest*, **60**, 585-599.
- Simmette, C. H. (1967) Childhood malignancies—report from a West African teaching hospital with special emphasis on Burkitt's tumor. *Clin Pediatr.*, **6**, 721-727.
- Stowens, D. (1966). *Pediatric Pathology* Second edition. Pp. 658-664. Baltimore: Williams and Wilkins.
- Varlend, S., Spicer, R. B. and Mackinnon, A. E. (1984). Teratoid Wilms' tumor *Cancer*, **53**, 1936-1942.
- Williams, A. O. (1975) Tumors of childhood in Ibadan, Nigeria. *Cancer*, **36**, 370-378.
- Williams, A. O. and Ajayi, O. O. (1976). Ultrastructure of Wilms' tumor (nephroblastoma) *Exp Mol Pathol*, **24**, 35-47.

The Authors

- E. E. U. Akang, MB,BS, FMCPPath, FWACP, Consultant Pathologist
- J. U. Okpala, MB,BS, Senior Registrar, Department of Paediatrics
- Y. Iliyasu, MB,BS, Registrar, Department of Pathology
- J. Lawani, MB,BS, FRCS, FMCS, FWACS, Cert Immunol, Consultant Urologist, Department of Surgery

Requests for reprints to E. E. U. Akang, Department of Pathology, University College Hospital, Ibadan, Nigeria.

Natural History of Obstructed and Pseudo-obstructed Megaureters Detected by Prenatal Ultrasonography

A. M. K. RICKWOOD, L. D. JEE, M. P. L. WILLIAMS and P. A. M. ANDERSON

Regional Department of Paediatric Urology, Royal Liverpool Childrens Hospital (Alder Hey), Liverpool

Summary—In a series of 38 patients with non-refluxing megaureters detected by prenatal ultrasonography, 89% were males and 16% had associated ipsilateral or contralateral urinary anomalies. By renographic criteria, 36% of ureters were not obstructed; renal function was never impaired initially and, on follow-up, spontaneous resolution of dilatation was common. Infective urinary calculi developed in 3 of the boys. In ureters obstructed by renographic or pressure-perfusion criteria, 79% exhibited normal renal function initially. Most such patients were managed expectantly; on follow-up, functional deterioration occurred in 2 patients, while in the remainder dilatation usually persists but without change in function.

Real or apparent pelviureteric junction (PUJ) obstruction is the commonest fetal uropathy detected by prenatal ultrasonography (Turnock and Shawis, 1984). Some 20% of cases are not obstructed by renographic criteria; here function is seldom, if ever, impaired (Arnold and Rickwood, 1990; Najmaldin *et al.*, 1991) and spontaneous resolution of dilatation is common. Function is usually well preserved in cases with renographic obstruction and rarely deteriorates in those managed expectantly (Ransley and Manzoni, 1985; Arnold and Rickwood, 1990; Madden *et al.*, 1991).

Also detected by prenatal ultrasonography, although less commonly, are examples of apparent primary vesicoureteric junction (VUJ) obstruction. Do these cases share the features of fetally diagnosed PUJ obstruction? Are a proportion not obstructed by renographic criteria and is renal function unaffected in this circumstance? Is function usually well preserved in the presence of renographic obstruction and, where this is so, is this maintained and is expectant management appropriate?

Patients and Methods

Patients with prenatally detected anatomical VUJ obstruction presenting from 1979 to mid-1991 were reviewed. Cystography was performed to exclude vesicoureteric reflux or bladder outflow obstruction. IVU was routine early in the series although not latterly. Most patients underwent dynamic diuresis renography, usually at about the age of 1 month. In a few cases, where IVU or ultrasonography suggested severe renal impairment, function was assessed by static, ^{99m}Tc DMSA scintigraphy, and obstruction by antegrade pressure-perfusion studies (Whitaker, 1973; Wentzell *et al.*, 1988).

Differential function of affected kidneys was assessed as glomerular filtration rate (^{99m}Tc DTPA), as effective renal plasma flow (^{125}I Hippuran, ^{99m}Tc MAG-3) or as differential uptake of isotope (^{99m}Tc DMSA). In cases bilaterally affected, or having a single functioning kidney, "differential" function was assessed in relation to normal, age-related values. Criteria for obstruction were as defined by O'Reilly *et al.* (1979) for renography and by Whitaker (1973) for pressure-perfusion examinations.

Conservatively managed patients did not receive

antibiotic prophylaxis and were reviewed, by ultrasonography, at 3-monthly intervals for the first year and 6-monthly thereafter. Renography was repeated at 12–24 months of age, depending on the sonographic findings. Urine cultures were obtained at routine visits and, whenever possible, during any febrile illness.

Results

General

Of the 38 patients, 34 (89%) were boys and the lesion was left-sided in 19 instances (50%) and bilateral in 5 (13%). Associated urinary anomalies comprised 2 examples of apparent PUJ obstruction ipsilaterally and, contralaterally, 1 each of renal agenesis, multicystic dysplasia, pelvic kidney and minor vesicoureteric reflux. The gestational age at which the anomaly had been detected, where known, was 16–19 weeks in 2 patients, 20–29 weeks in 3 patients and 30–40 weeks in 17 patients.

None of the patients had symptoms neonatally and only 2 had a relevant physical sign (palpable kidney). Ureteric dilatation on IVU or ultrasonography was rated as mild in 2 patients, moderate in 26 and severe in 10.

Three patients early in the series did not have renography while a more recent case, with severe renal impairment, has been assessed only by ^{99m}Tc DMSA scintigraphy.

Patients without obstruction

There were 13 patients without obstruction, all detected by renography, and 1 by renography and perfusion studies. Of these, 2 had bilateral involvement. Function in affected kidneys was unimpaired. All were managed expectantly in the first instance and their progress is summarised in Fig. 1. Two boys with documented urinary infection, plus another with probable infection, developed urinary calculi (Rickwood and Reiner, 1991). The remainder have been asymptomatic and free of urinary infection during follow-up ranging from 3–75 months (mean 35).

Patients with obstruction

There were 21 patients with obstruction, 18 detected by renography, and 4 by renography and/or pressure-perfusion studies. Of these, 3 had bilateral involvement and 2 had ipsilateral apparent PUJ obstruction. Among 24 affected kidneys, differential function exceeded 40% in 19 (79%) and was 20–40% in 5 (21%).

The progress of these patients is summarised in Figure 2. Routine policy was to undertake early elective ureteric reimplantation (usually with distal ureteric tailoring) only in the presence of impaired function, although 2 patients with additional apparent PUJ obstruction had normal function. The anatomical outcome of these procedures has been excellent in all but 1 instance, although functionally there has been only marginal improvement in the 3 patients reassessed so far. One girl, with 37% differential function initially, was lost to follow-up and when re-presenting at 4 years of age with urinary infection, was found to have spontaneous resolution of the hydroureteronephrosis and functional improvement to 45% differential.

A total of 14 patients with unimpaired function initially were managed expectantly in the first instance. In 2, where there had been no urinary infection or change in sonographic appearances, function had declined at reassessment (43% to 19% at 13 months, 55% to 27% at 18 months); function

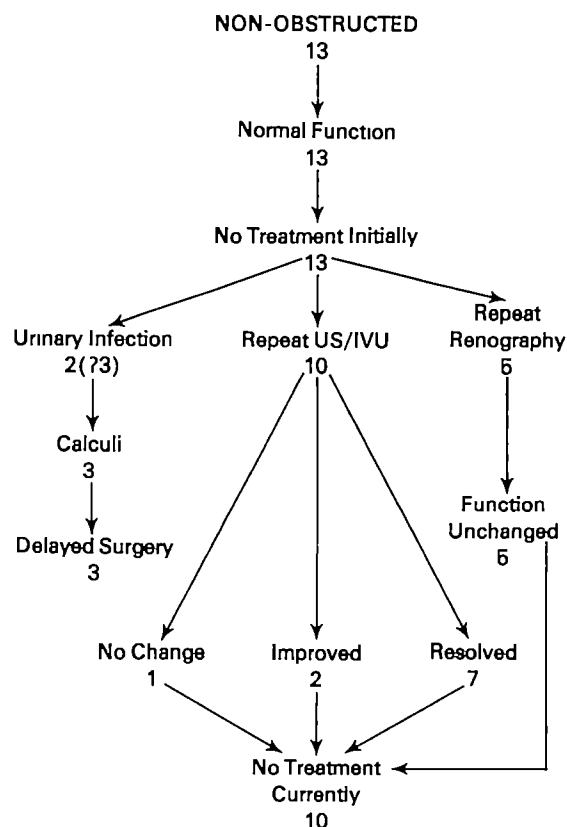


Fig. 1 Progress of 13 patients (15 ureters) without obstruction by renographic criteria.

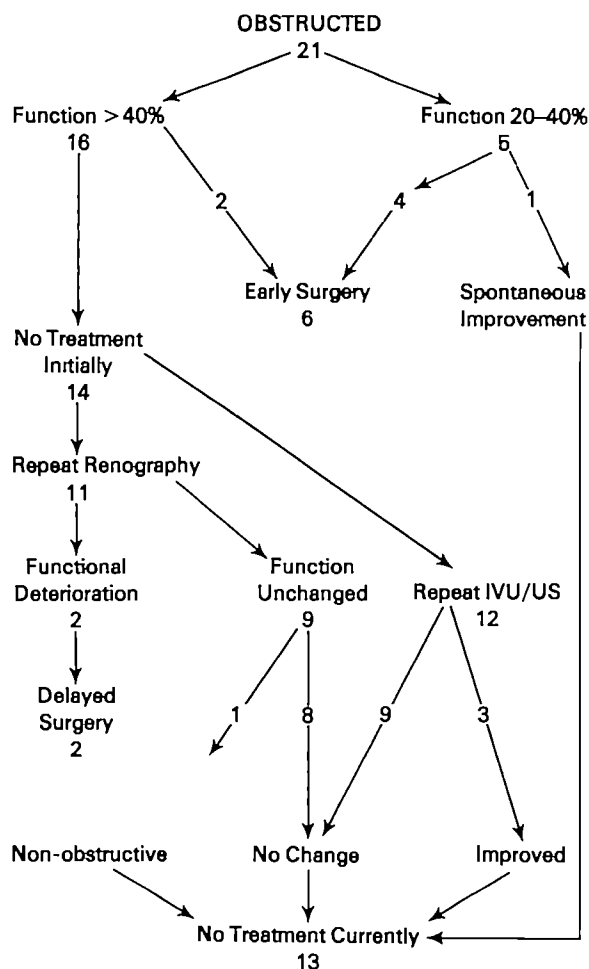


Fig. 2 Progress of 21 patients (24 ureters) with obstruction by renography and/or pressure-perfusion studies.

has yet to be assessed following successful ureteric reimplantation. Twelve patients continue to be managed expectantly over periods ranging from 3 to 60 months (mean 28). In the majority appearances remain unchanged, as does function in those re-examined by renography. Symptomatic urinary infections occurred in 3 patients.

Discussion

As is evident, fetally diagnosed non-refluxing megaureters are often not obstructed by renographic criteria, the proportion, 36% (15 of 39 ureters), being almost twice that found with antenatally detected PUJ "obstruction" (Arnold

and Rickwood, 1990). As with the latter, function in this circumstance seems not to be affected neonatally, nor has it declined since in those reassessed, while the dilatation itself exhibits a general trend towards spontaneous resolution. The only non-benign feature in these patients is the risk of infective stone formation in a minority of males (Rickwood and Reiner, 1991).

In patients with obstruction by renographic or pressure-perfusion criteria, function is also usually well preserved (>40% differential) initially, the proportion, 79% (19 of 24 ureters), closely approximating to that found in prenatally diagnosed and renographically confirmed PUJ obstruction (Arnold and Rickwood, 1990; Madden *et al.*, 1991).

Where there was impaired function initially, any improvement following surgical intervention has been marginal and indeed the best outcome occurred in 1 girl inadvertently managed expectantly. Our surgical intervention was relatively late, at 2–6 months of age, and arguably a better result would have been obtained by ureteric reimplantation neonatally as advocated by Peters *et al.* (1989), although in that series the functional, rather than anatomical, results were ill-defined and were obtained at the expense of an appreciable incidence of anaesthetic complications and secondary vesicoureteric reflux.

Is expectant management appropriate where function is unimpaired? Spontaneous functional deterioration would appear to be unusual (Keating *et al.*, 1989), although the present series contains 2 examples of silent and appreciable decline. Anatomically there has been little tendency towards spontaneous improvement and so long as dilatation persists there is a risk of urinary infection, as has occurred in some cases, and potentially, stone formation or late functional deterioration. The question posed cannot yet be answered and warrants a clinical trial. It would nonetheless appear that early intervention is unnecessary and that if routine ureteric reimplantation ultimately proves to be the superior option, then this can safely be deferred for several months, so enabling a technically easier procedure and, perhaps, a better result.

References

- Arnold, A. J. and Rickwood, A. M. K. (1990). Natural history of pelviureteric junction obstruction detected by prenatal ultrasonography. *Br. J. Urol.*, **65**, 91–96.
- Keating, M. A., Escala, J., Snyder, H. M. *et al.* (1989). Changing concepts in management of primary obstructive megaureter. *J. Urol.*, **142**, 636–640.

- Madden, N. P., Thomas, D. F. M., Gordon, A. C. et al.** (1991). Antenatally detected pelviureteric junction obstruction. Is non-operation safe? *Br. J. Urol.*, **68**, 305–310.
- Najmaldin, A. S., Burge, D. M. and Atwell, J. D.** (1991). Outcome of antenatally diagnosed pelviureteric junction hydronephrosis. *Br. J. Urol.*, **67**, 96–99.
- O'Reilly, P. W., Lawson, R. S., Shields, R. A. et al.** (1979). Idiopathic hydronephrosis—the diuresis renogram: a new non-invasive method of assessing equivocal pelviureteric obstruction. *J. Urol.*, **121**, 153–157.
- Peters, C. A., Mandell, J., Lebowitz, R. L. et al.** (1989). Congenital obstructed megaureters in early infancy: diagnosis and treatment. *J. Urol.*, **142**, 641–645.
- Ransley, P. G. and Manzoni, G.** (1985). Extended role of DTPA scan in assessing function and PUJ obstruction in neonates. *Dialogues in Pediatric Urology*, **8**, 6–8.
- Rickwood, A. M. K. and Reiner, I.** (1991). Urinary stone formation in children with prenatally diagnosed uropathies. *Br. J. Urol.*, **68**, 541–542.
- Turnock, R. R. and Shawis, R.** (1984). Management of fetal urinary tract anomalies detected by prenatal sonography. *Arch. Dis. Child.*, **59**, 962–965.
- Wentzell, P. G., Arnold, A. J., Carty, H. et al.** (1988). Two-needle modification of the Whitaker test. *Br. J. Urol.*, **62**, 388–389.
- Whitaker, R. H.** (1973). Methods of assessing obstruction in dilated ureters. *Br. J. Urol.*, **45**, 15–22.

The Authors

A. M. K. Rickwood, MA, FRCS, Urological Surgeon.
 L. D. Jee, FCS(SA)(Urol), Herbert Johnston Research Fellow.
 M. P. L. Williams, FRCS, Senior Surgical Registrar.
 P. A. M. Anderson, FRCS(C), Herbert Johnston Research Fellow.

Requests for reprints to: A. M. K. Rickwood, Regional Department of Paediatric Urology, Royal Liverpool Children's Hospital (Aldey Hey), Eaton Road, Liverpool L12 2AP.

Case Reports

Unusual Presentation of Adult Posterior Urethral Valve

R. KAPOOR, A. TEWARI and V. K. MISHRA, *Department of Urology, Sanjay Gandhi Post-Graduate Institute of Medical Sciences, Lucknow, India*

A case of adult posterior urethral valve presenting with recurrent gravelluria and multiple urethral and ureteric calculi is reported.

Case Report

A 27-year-old male presented with a 5-year history of recurrent urinary tract infection, gravelluria and straining during micturition.

Serum creatinine was normal. The urine contained red blood cells, 20–30 pus cells/hpf and *Escherichia coli*. Plain X-ray revealed bilateral lower ureteric calculi and a bunch of stones within the prostatic urethra. Micturating cystourethrography revealed a dilated prostatic urethra and no evidence of vesicoureteric reflux (Fig. 1). A



Fig. 1



Fig. 2

retrograde urethrograph showed multiple radiolucent defects in the prostatic urethra (Fig. 2).

Cystourethroscopy demonstrated multiple sago-like stones enmeshed in matrix in the dilated prostatic urethra. They were washed away without difficulty. Endoscopy revealed thick cusped type I posterior urethral valves which were retaining the stone mass. The posterior urethral valve was fulgurated and the ureteric stones were removed endoscopically at a later date. Post-operative recovery was uneventful. Follow-up 16 months later revealed a mean flow rate of 17 ml/s with complete emptying of the bladder, and reduced dilatation of the prostatic urethra.

Comment

Adult posterior urethral valves are rare and patients usually present with bilateral hydronephrosis and renal failure (Marsden, 1969; Martin *et al.*, 1977). Occasionally they may present with incontinence or a dilated Cowper's gland (Drouin *et al.*, 1979).

References

- Drouin, G., Laperriere, J. and Gregoire, A. (1979). Urethral valves as a cause of dilated Cowper's glands and perineal pain. *J. Urol.*, **120**, 634–635.
- Marsden, R. T. H. (1969). Posterior urethral valves in adults. *Br. J. Urol.*, **41**, 586–591.
- Martin, J., Anderson, J. and Raz, S. (1977). Posterior urethral valves in adults: a report of 2 cases. *J. Urol.*, **118**, 978–979.

Requests for reprints to: R. Kapoor, Department of Urology, Sanjay Gandhi Post-Graduate Institute of Medical Sciences, P.B. 375, Raebareli Road, Lucknow 226 001, India.

Pelvic Lipomatosis or Pericystitis Plastica?

C. F. HEYNS and F. J. ALLEN, *Department of Urology, Tygerberg Hospital and Faculty of Medicine, University of Stellenbosch, Tygerberg, South Africa*

Pelvic lipomatosis, an unusual condition in which the bladder is surrounded by an excess of mature fatty tissue, varies in severity but can result in severe obstructive uropathy (Crane and Smith, 1977). The typical radiographic findings include a tear-drop shaped deformity of the bladder and extrinsic compression of the rectum.

Case Report

R.B., a 32-year-old black male, presented in September 1986 with dysuria, frequency and a painful left testis. His past medical history was significant only for a laparotomy performed in 1983 for an abdominal stab wound. Physical examination revealed tenderness of the perineum, prostate and left testis. Urine microscopy showed scanty leukocytes, but no growth. Intravenous urography, micturating cystourethrography and cystoscopy were normal. Thereafter he was seen intermittently with the same complaints but did not attend regularly for follow-up.

In September 1989 he was seen with a complaint of severe perineal pain. Physical examination again revealed no abnormality. Urine microscopy and culture were negative but the erythrocyte sedimentation rate was 80 mm/h (Westergren). Cystoscopy now revealed elongation of the prostatic urethra with antero-superior displacement of the bladder base and biopsies showed chronic inflammation with cystitis cystica and glandularis. A meglumine amidotrizoate enema revealed rectal narrowing suggestive of extrinsic compression (Fig. 1). A micturating cystourethrogram showed a pear-shaped deformity of the bladder and a diagnosis of pelvic lipomatosis was considered. Computed tomography (CT) was consistent with this diagnosis, but magnetic resonance imaging (MRI) did not show any excess of fatty tissue (Fig. 2). An exploratory laparotomy was then performed. At surgery a severe fibrotic reaction was found surrounding the bladder, the wall of which was grossly thickened. Biopsies of the bladder and perivesical tissue revealed a dense fibrous reaction with only scattered mature fat cells. The patient was symptomatically much improved after the laparotomy.

Comment

Although in the early reports surgical exploration was used to confirm the diagnosis of pelvic

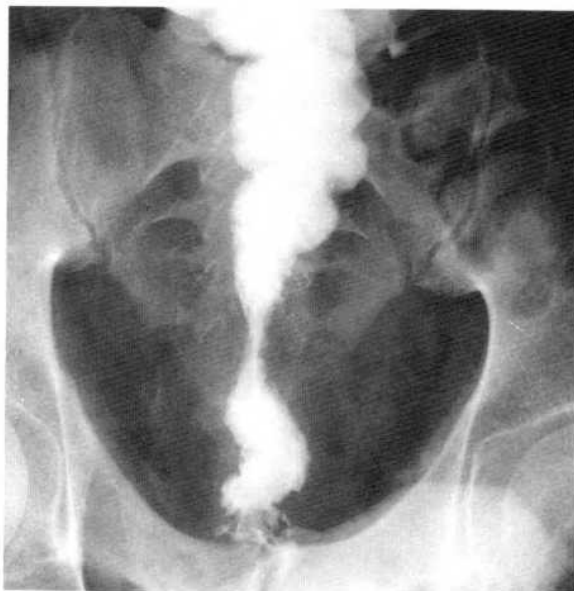


Fig. 1 Meglumine amidotrizoate enema suggesting external compression of the rectum.



Fig. 2 Magnetic resonance imaging demonstrates no excess of fatty tissue in the pelvis.

lipomatosis, it has more recently become accepted that CT is sufficient to confirm the diagnosis (Werboff *et al.*, 1979). In our patient the diagnosis of pelvic lipomatosis was suggested by contrast enema, cystography, cystoscopy and supported by CT. MRI, however, which has been suggested as the ideal imaging method in this condition (Allen and De Kock, 1987), did not demonstrate an

abnormal amount of fat in the pelvis. Hewett and Headstream (1960) first used the term pericystitis plastica to describe a condition pathologically similar to primary retroperitoneal fibrosis, but localised to the pelvis. The marked similarity between the two conditions must raise doubt as to the validity of reported cases of pelvic lipomatosis where CT has been used as the definitive investigation.

References

- Allen, F. J. and De Kock, M. L. S. (1987). Pelvic lipomatosis: the nuclear magnetic resonance appearance and associated vesicoureteral reflux. *J. Urol.*, **138**, 1228–1230.
- Crane, D. B. and Smith, M. J. V. (1977). Pelvic lipomatosis: 5-year follow-up. *J. Urol.*, **118**, 547–550.
- Hewett, A. L. and Headstream, J. W. (1960). Pericystitis plastica. *J. Urol.*, **83**, 103–107.
- Werboff, L. H., Korobkin, M. and Kelin, R. S. (1979). Pelvic lipomatosis: diagnosis using computed tomography. *J. Urol.*, **122**, 257–259.

Requests for reprints to: C. F. Heyns, Department of Urology, Faculty of Medicine, University of Stellenbosch, P.O. Box 63, Tygerberg 7505, South Africa.

Mesothelioma of the Tunica Vaginalis of the Testis

J. G. NOBLE, A. WATKINS, M. E. CHAPPELL and A. D. HEATH, *Departments of Surgery and Histopathology, Southend General Hospital, Southend on Sea*

Case Report

A 62-year-old man presented with a 3-month history of a painless, left-sided scrotal swelling. He had undergone surgery for a left-sided hydrocele 9 years previously. Clinical examination revealed a hydrocele with a palpably normal testis and these findings were confirmed on an ultrasound scan.

The hydrocele was explored through a scrotal incision and the tunica vaginalis was noted to be thickened with multiple papillary nodules on its parietal surface. An area was excised and sent for histology and the hydrocele excised in standard fashion.

Microscopy revealed a cellular papillary lesion with nuclear pleomorphism, frequent mitoses and little stroma in the papillary cores characteristic of a malignant mesothelioma. Immunoperoxidase staining for prostatic specific antigen and other carcinoma markers was negative (Fig.).

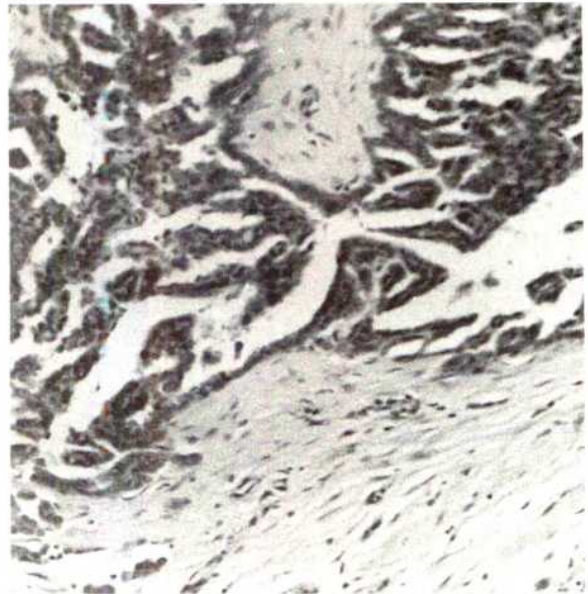


Fig. Papillary mesothelioma infiltrating connective tissue and exhibiting nuclear pleomorphism and high mitotic rate. (H and E $\times 125$).

In view of this finding the patient subsequently underwent a left orchietomy via an inguinal approach together with a wide excision of the left hemiscrotum.

Comment

Mesothelioma is an uncommon tumour arising from the serosal surfaces of the pleural, pericardial and peritoneal cavities. Although the tunica vaginalis is an extension of the peritoneum, tumours arising from this tissue are very rare. The peak incidence of presentation is in the seventh decade. A hydrocele is the most common presenting feature (Prescott *et al.*, 1988), making the pre-operative diagnosis of the condition difficult. Ultrasound scanning, as in this case, can highlight a thickened tunica and occasionally identify larger pedunculated lesions. Cytological analysis of hydrocele fluid has been positive in one case only (Japko *et al.*, 1982).

Patients who are treated without evidence of distant metastases have a good prognosis (Fitzmaurice *et al.*, 1987) but the response of mesothelioma in advanced disease is poor to both chemotherapy and radiotherapy.

This case emphasises the need for careful evaluation of all patients presenting with a hydrocele in order to treat this potentially serious condition without delay.

References

- Fitzmaurice, H., Hotiana, M. Z. and Crucioli, V. (1987). Malignant mesothelioma of the tunica vaginalis testis. *Br. J. Urol.*, **60**, 184.
- Japko, L., Horta, A. A., Schreiber, K. *et al.* (1982). Malignant mesothelioma of the tunica vaginalis testis. *Cancer*, **49**, 119–127.
- Prescott, S., Taylor, R. E., Sclare, G. *et al.* (1988). Malignant mesothelioma of the tunica vaginalis testis: a case report. *J. Urol.*, **140**, 623–624.

Requests for reprints to: J. G. Noble, Department of Urology, Middlesex Hospital, Mortimer Street, London W1N 8AA.

Leukaemic Infiltration, Paracoccidioidomycosis and Nodular Hyperplasia of the Prostate

C. R. MELO, I. S. MELO and C. T. CERSKI, *Departments of Pathology, Federal Universities of Santa Maria and Rio Grande do Sul, Santa Maria and Porto Alegre, Brazil*

Case Report

A 71-year-old white man sought medical attention in 1987 with a recent history of weakness, night sweats and weight loss. His white blood cell count was 82,800 with thrombocytopenia and anaemia. Physical examination revealed bilateral cervical and axillary lymphadenopathy and splenomegaly. Bone marrow aspiration was diagnostic of chronic lymphocytic leukaemia (CLL). He achieved a haematological remission with chemotherapy (Leukeran and Meticorten) from February 1988 to May 1989, although lymphadenopathy and splenomegaly persisted. In April 1989 he developed acute urinary retention with dysuria and suprapubic discomfort. Rectal examination showed prostatic enlargement and histological examination of a transrectal prostatic core biopsy showed granulomatous inflammation associated with lymphocytic infiltrate (Figs 1 and 2). Gomori silver methenamine stained sections disclosed numerous multibudding organisms (Fig. 1, inset). Immunohistochemistry with the avidin-biotin-antiperoxidase method using rabbit polyclonal antihuman *Paracoccidioides brasiliensis* antibody confirmed the diagnosis. Treatment with 400 mg oral ketoconazole daily was started and in June 1989 the prostate was resected. The chips submitted for histological examination revealed nodular prostatic hyperplasia with a nodular lymphocytic infiltrate and many granulomas containing multibudding yeast forms. Other foci of paracoccidioidomycosis (PCM) were found neither in the lungs nor elsewhere in the body.

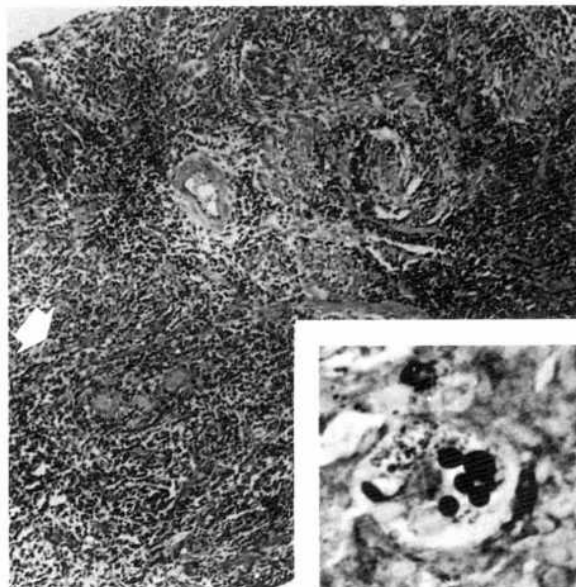


Fig. 1 Needle biopsy of the prostate showing small granulomas (arrow) and lymphocytic infiltrate (H and E $\times$ 100). Inset: yeast organisms (GMS $\times$ 400).

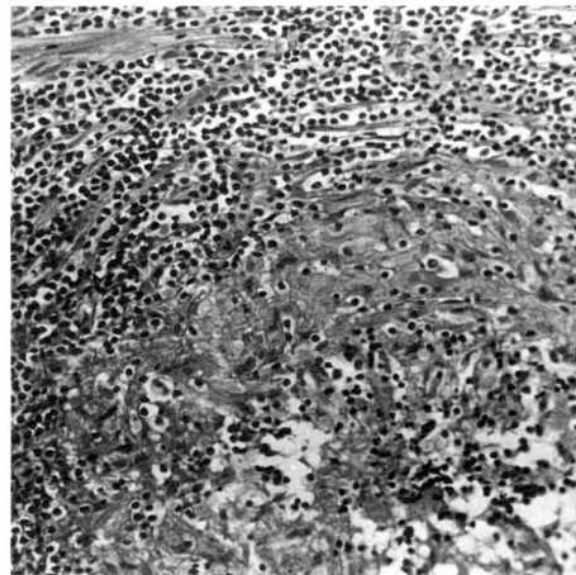


Fig. 2 Granuloma at bottom right is surrounded by the leukaemic infiltrate. (H and E $\times$ 250).

Comment

In leukaemic patients urinary symptoms may be due to leukaemic meningeal involvement or to leukaemic infiltration of the prostate. The latter is a rare manifestation of leukaemia and is usually

found in known cases of leukaemia, but it may be the first clinical manifestation of an undiagnosed leukaemia (*Sridhar and Woodhouse, 1983*).

According to the histological type of leukaemia, relief of symptoms may be achieved with chemotherapy or radiotherapy (*Merimsky et al., 1981*). In CLL, however, prostatic resection with haematological support is usually a safe and effective treatment.

PCM is a systemic mycosis that starts as a pulmonary infection after inhalation of the causal agent. It tends to remain subclinical and pulmonary lesions may be invisible on chest X-ray. Dissemination to other organs, including the genitourinary tract, occurs early in the pulmonary phase and can remain dormant for years (*Cechella et al., 1982*).

References

- Cechella, M. S., Melo, C. R., Melo, I. S. et al.* (1982). Paracoccidioidomycose genital masculina. *Rev. Inst. Med. Trop. São Paulo*, **24**, 240–245.
- Merimsky, E., Baratz, M. and Kahn, Y.* (1981). Leukaemic infiltration of the prostate. *Br. J. Urol.*, **53**, 150–151.
- Sridhar, K. N. and Woodhouse, C. R. J.* (1983). Prostatic infiltration in leukaemia and lymphoma. *Eur. Urol.*, **9**, 153–156.

Requests for reprints to: C. R. Melo, Department of Pathology, Federal University, 97, 119 Santa Maria, RS, Brazil.

Ureteric-Anal Canal Fistula Secondary to Ureteric Calculus

U. V. SATHAYE, K. V. SHAH and K. P. PARIKH, *Division of Urology, Institute of Kidney Diseases and Research Centre, Ahmedabad, India*

Case Report

A 14-year-old boy presented with a 3-year history of continuous urinary leak from the anus; he had a normal voiding pattern and faecal continence. Two months previously he had undergone an anal fistulectomy for the same leak which was from a perianal site at that time.

General examination was unremarkable. Local examination showed a continuous urinary leak from the anus and perianal scarring due to previous surgery.

Investigations revealed normal renal function. A urine culture was sterile. Plain X-ray showed a large opaque stone in the line of the right lower ureter. IVU showed a normal left upper tract and right hydroureteronephrosis due to a lower ureteric stone (Fig. 1). Examination under

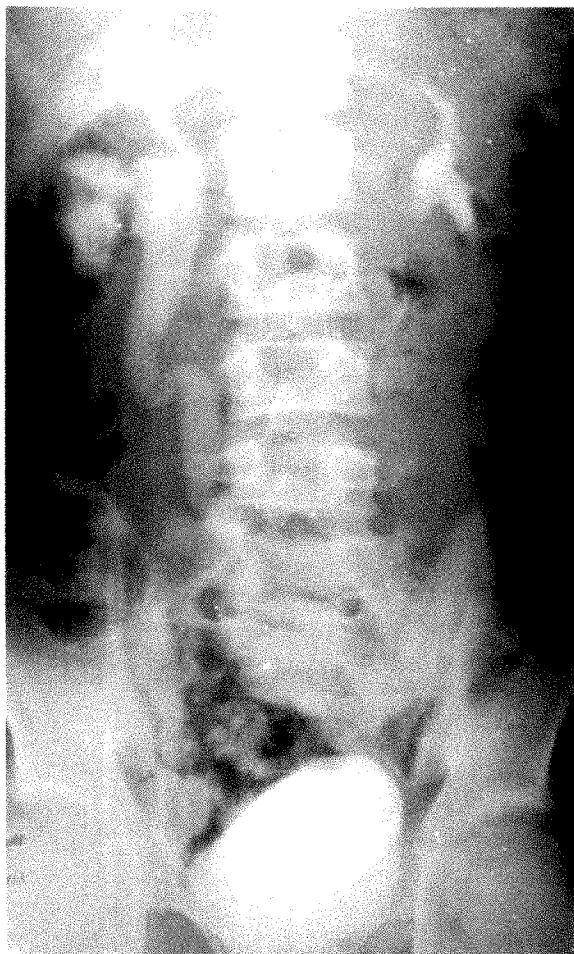


Fig. 1



Fig. 2

anaesthesia showed that the urinary leak came from an opening 2 cm above the anal verge, which could be cannulated up to 5 cm. Cystourethroscopy was unremarkable except for an oedematous right ureteric orifice. A fistulogram revealed a wide bifurcated tract up to the stone with filling of the right ureter and bladder (Fig. 2). A micturating cystourethrogram was normal.

At exploration, the 4-cm bifid fistulous tract containing the 2 large stones was completely excised and the dilated proximal ureter was reimplanted into a Boari bladder tube. Post-operative recovery was uneventful. An IVU 3 months later showed complete regression of the right hydroureteronephrosis.

Comment

Ureteric fistulas are usually a result of infection, inflammation or stones (Sathaye *et al.* 1988). Fistulas with the lower gastrointestinal tract are very rare (Kar *et al.*, 1984). To the best of our knowledge, a fistula between the ureter and anal canal has not been previously reported. In our patient the impacted stone had probably created local infection and an abscess which burst perianally. The fistulectomy for the misdiagnosed fistula *in ano* caused the opening to recede into the anal canal. Because of the calculus the inflammation and fistula persisted.

References

- Kar, A., Angwafo, F. F. and Jhonhewala, J. S. (1984). Ureteroarterial and ureteroanmoid fistula associated with polyethylene indwelling ureteral stents. *J. Urol*, 132, 755-757.
Sathaye, U. V., Dodia, V. B. and Mehta, J. M. (1988). Ureterovasal fistula with calculi. *Indian J Surg*, 50, 373.

Requests for reprints to: U. V. Sathaye, Consultant Urologist, Opposite Medical College, Solerium Road, Jamnagar 361 008, India.

Leiomyoma of the Renal Pelvis

A O'BRIEN, B. SINNOTT, P. McLEAN and G. D. DOYLE,
Departments of Urology and Histopathology, Beaumont Hospital, Dublin, Ireland

Case Report

A 43-year-old lady was referred with a history of left loin pain and intermittent frank haematuria. Clinical examination revealed left renal angle tenderness.

Intravenous urography showed minimal function from an atrophic right kidney. The upper pole calices of the left kidney were distorted and dilated. Ultrasonography confirmed an atrophic right kidney and revealed a cyst, 5 cm in diameter, in the posterolateral aspect of the upper pole of the left kidney. Medial to the cyst was a lobulated area of soft tissue echogenicity, measuring 3.5 x 2 cm, adjacent to the dilated upper pole calices. Retrograde ureterography revealed a filling defect at the infundibulum of the upper pole calices. At ureteroscopy the filling defect was seen to be caused by a rounded, smooth, dark-coloured lesion on the renal pelvic wall, almost completely occluding the infundibulum of the upper pole calices.

On exploration a cyst was found in the upper pole of the kidney. The cyst was readily separable from adjacent renal parenchyma and was found to be contiguous with the solid, firm lesion arising from the pelvic wall at the infundibulum of the upper pole calices. The pelvicaliceal system was otherwise macroscopically normal. The lesion and cyst were resected *en bloc* by an upper pole partial nephrectomy (Fig. 1).

The patient made a satisfactory recovery.

Histological examination showed the cyst to be lined by a low cuboidal epithelium. The solid lesion (Fig. 2) consisted of uniform spindle cells arranged in bundles coursing in various directions and in places exhibiting a palisading pattern. The nuclei of uniform morphology had blunted ends and were surrounded by a distinctly eosinophilic cytoplasm. Mitotic figures were infrequent. Examination of PTAH preparations under oil revealed longitudinal intracytoplasmic filaments. Positivity for tumour markers, including vimentin, desmin and muscle specific actin, was demonstrated.

The tumour showed the features of a leiomyoma on electron microscopy.

Comment

Renal leiomyomas are uncommon tumours and have been categorised into 3 groups, depending mainly on their site within the kidney, and thereby the location of the smooth muscle cells from which they are likely to have arisen (Belis *et al.*, 1979).

In the most common group the leiomyomas are on the cortical surface or in the most superficial cortex and are considered to arise from smooth muscle cells in the renal capsule. They are usually multiple and small, measuring only a few millimetres in diameter. They show no predilection for either gender and do not cause any symptoms, having generally been coincidental findings at autopsy or surgical exploration.

In contrast, the second category comprises solitary tumours which have attained large proportions, weighing up to 5 kg. While their large dimensions have not infrequently rendered their exact site of origin difficult to determine, they are

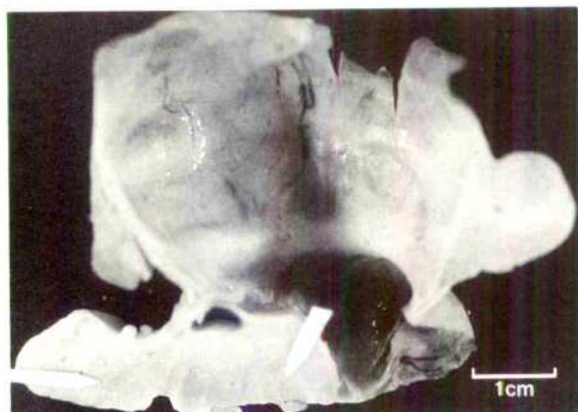


Fig. 1 Gross appearance of specimen as seen from the renal pelvis. Lesion outlined by arrows.

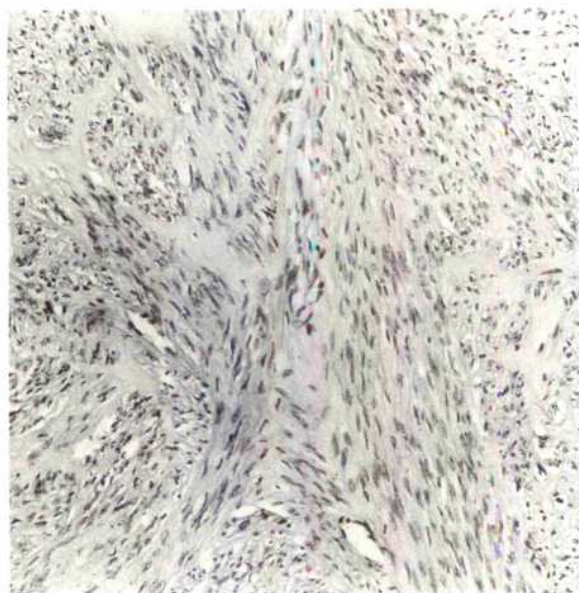


Fig. 2 Section showing uniform spindle cells lying parallel and arranged in bundles which course in various directions. (H and E $\times 200$).

believed to arise from cortical vascular smooth muscle cells. They usually give rise to flank pain or discomfort, though their diagnosis has occasionally followed the finding of an asymptomatic abdominal mass. They occur almost invariably in females, and in all age groups, including the newborn (Zuckermann *et al.*, 1947).

Leiomyomas arising from smooth muscle of the renal pelvic wall are rare, only 5 patients having been previously reported (Kho and Duggan, 1989). All were women, aged between 24 and 50 years,

who presented with either pain or haematuria and were found to have renal pelvic filling defects on intravenous urography. All of the previously reported patients were presumed to have transitional cell tumours which were resected by nephroureterectomy.

Our patient is the only one to have presented with both pain and haematuria. Since the contralateral kidney was barely functional, maximal preservation of functioning renal parenchyma was desirable. The ureteroscopic appearance of the renal pelvic lesion was reassuring, as it was considered that the tumour was unlikely to be a transitional cell carcinoma. This is the only reported case of renal pelvic leiomyoma to have been resected by partial nephrectomy. The gross, microscopic and immunohistochemical features were similar to those reported previously. However, it is the only case to have been associated with cyst formation.

References

- Belis, J. A., Post, G. J., Rochman, S. C. *et al.* (1979). Genitourinary leiomyomas. *J. Urol.*, **123**, 424–429.
- Kho, G. T. and Duggan, M. A. (1989). Bizarre leiomyoma of the renal pelvis with ultrastructural and immunohistochemical findings. *J. Urol.*, **141**, 928–929.
- Zuckermann, I. C., Kershner, D., Laytner, B. D. *et al.* (1947). Leiomyoma of the kidney. *Ann. Surg.*, **126**, 220–228.

Requests for reprints to: A. O'Brien, Department of Urology, Craigavon Area Hospital, Craigavon, N. Ireland.

Ureterocolic Fistula due to Impacted Ureteric Stone

K. P. PATIL, S. D. SHETTY, N. ANANDAN and A. IBRAHIM, *Department of Urology, College of Medicine, King Saud University (Abha), and Asir Central Hospital, Abha, Saudi Arabia*

Ureteric fistulas are usually ureterovaginal and ureterocutaneous, but ureteroarterial and ureteroarterio-enteric fistulas have been reported following aortoiliac bypass graft surgery (Kar *et al.*, 1984). Ureteroenteric fistulas are very rare. We report a case of ureterocolic fistula caused by an impacted ureteric calculus.

Case Report

A 40-year-old Saudi male was referred with a history of

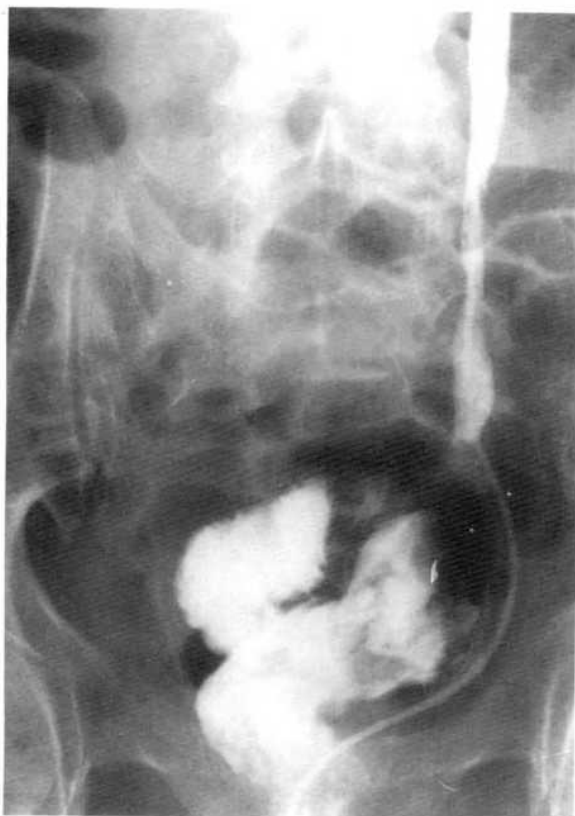


Fig. Retrograde ureteropyelogram showing fistulous tract and the ureteric stone.

dysuria. There were no other urinary symptoms and clinical examination was unremarkable. The urine contained significant gram-negative bacteria but no acid fast bacilli. Investigations revealed a non-functioning left kidney, with a 5-cm renal stone and a 1.5-cm ureteric stone just below the left sacroiliac joint. The right kidney showed compensatory hypertrophy. Ultrasonography revealed a small left kidney with a dilated collecting system. At cystoscopy a 6 F ureteric catheter was passed into the left ureter and was initially held up at the 8-cm level, but subsequently could be advanced up to the kidney. The retrograde ureteropyelogram showed a dilated pelvicaliceal system with a calculus in the upper major infundibulum. The ureter was dilated up to the calculus (Fig.), just proximal to which the dye was seen passing medially into the colon. A barium enema showed that the sigmoid loop was tethered at the level of the ureteric calculus. Sigmoidoscopy was normal.

On exploration, the kidney was found to be adherent to the surrounding tissue and the ureter was dilated and thickened up to the site of the calculus. A small fistulous tract was seen communicating with the sigmoid colon. Nephrectomy was performed with excision of the ureter distal to the impacted stone. The tract was disconnected

and transfixed with 2/0 chromic catgut. There was no pathology in the sigmoid colon. The patient made an uneventful recovery and was free from dysuria. Histologically the kidney showed features of xanthogranulomatous pyelonephritis and the ureter showed chronic inflammatory fibrosis.

Comment

The classical symptoms of ureteroenteric fistula, such as pneumaturia, faecaluria and diarrhoea (Heney and Crooks, 1984), were not seen in our patient, probably because of the impacted ureteric calculus.

References

- Heney, N. M. and Crooks, K. K. (1984). Ureterocolic fistula. *Br. J. Urol.*, **56**, 225-226.
- Kar, A., Angwafo, F. F. and Jhunjhuwala, J. S. (1984). Ureteroarterial and ureterosigmoid fistula associated with polyethylene ureteral stents. *J. Urol.*, **132**, 755-757.

Requests for reprints to: K. P. Patil, Department of Urology, Asir Central Hospital, P.O. Box 34, Abha, Saudi Arabia.

Choriocarcinoma Arising in Transitional Cell Carcinoma of the Bladder

A. L. FOWLER, ELIZABETH HALL and G. REES,
Departments of Pathology and Oncology, Royal United Hospital, Bath

Case Report

A 74-year-old man was referred for radical radiotherapy for a T3 transitional cell carcinoma. After the start of radiotherapy he complained of breast tenderness and was noted to have bilateral gynaecomastia (Campo *et al.*, 1989). The serum beta-HCG concentration was 15,000 iu/l.

His gynaecomastia became more prominent and shortly after completing radiotherapy there was evidence of distant metastases and consequent rapid decline in his condition. Owing to the possibility of this being a germ cell tumour he was treated with etoposide but with no response. At this stage his beta-HCG had risen to 75,000 iu/l. At autopsy there was evidence of spread to neck nodes, thyroid, lungs and mediastinum, gut, kidney, adrenal glands and liver as well as spinal involvement, scalp, meningeal and choroidal spread. The overall tumour bulk was extremely large.

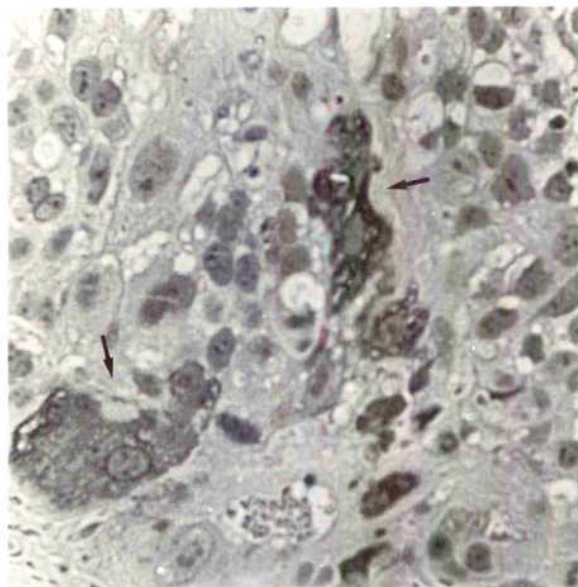


Fig. Poorly differentiated urothelial carcinoma of bladder with cells producing HCG (arrows). (Anti-human chorionic gonadotrophin (Avidin Biotin Complex) $\times 128$).

A serial increase in positive staining for beta-HCG, together with the appearance of choriocarcinoma cells, was demonstrated in successive biopsies (Fig.). The original biopsy showed absence of both.

Comment

About 12 cases of choriocarcinoma arising in bladder tumour have been reported since 1904. A suggested mechanism is "retrodifferentiation" (Abratt *et al.*, 1959) during progression of the tumour. This is not the same as primary choriocarcinoma arising in the bladder from germinal rests. Non-gestational choriocarcinoma does not show the excellent response to chemotherapy seen in the gestational type. Various combinations, including platinum compounds, have not been effective in previously reported cases (Burry *et al.*, 1986). Measurement of beta-HCG may be a useful way of detecting these aggressive tumours early so that treatment can be suitably adjusted, and for deciding prognosis.

References

- Abratt, R. P., Temple-Camp, C. R. E. and Pontin, A. R. (1989). Choriocarcinoma and transitional cell carcinoma of the bladder—a case report and review of the clinical evolution of disease in reported cases. *Eur. J. Surg. Oncol.*, **15**, 149–153.
- Burry, A. F., Munn, S. F., Arnold, E. P. *et al.* (1986). Trophoblastic metaplasia in urothelial carcinoma of the bladder. *Br. J. Urol.*, **58**, 142–146.
- Campo, E., Algaba, F., Palacin, A. *et al.* (1989). Placental proteins in high-grade urothelial neoplasms. *Cancer*, **63**, 2497–2504.

Requests for reprints to: A. L. Fowler, 42B Cautley Avenue, Clapham, London SW4 9HU.

Correspondence

Dear Sir,

re Effect of catheter material on the incidence of urethral strictures. G. S. M. Robertson *et al.* *Br. J. Urol.*, **68**, 612-617, 1991.

In this retrospective study of 299 patients undergoing transurethral prostatectomy, Robertson and his co-workers have determined that there is no difference in the rate of urethral stricture formation in men catheterised with Eschmann Folatex (latex) catheters compared to the rate of strictures following catheterisation with Simplastic (PVC) catheters. We believe it is incorrect for Robertson *et al.* to conclude as a result of these findings that there is no apparent advantage in the use of non-latex catheters for men undergoing short-term urethral catheterisation.

The association between urinary catheter toxicity, urethritis and urethral stricture formation has been proven following carefully planned and controlled studies by different groups of researchers (Ruutu *et al.* *Br. J. Urol.*, **57**, 82-87, 1985; Talja *et al.* *Br. J. Urol.*, **57**, 579-584, 1985; Nacey and Delahunt. *N.Z. Med. J.*, **104**, 355-356, 1991). Historically, toxicity has been associated with latex catheters and is thought to be caused by catalysts, monomers or various additives used in the polymerisation process (Blacklock. *Br. J. Urol.*, **58**, 475-478, 1986). In an attempt to prevent the leaching of these compounds some manufacturers have coated the surface of the catheters with teflon or silicone. It must be emphasised that not all latex catheters are toxic. Many non-toxic latex catheters are available for clinical use and most of the major manufacturers are able to provide evidence as to the non-toxicity of their products as determined by cell culture testing (Standards Association of Australia (1984). *Single Use Urethral Catheters (Sterile) for General Medical Use*. AS2696. Sydney). Toxicity is not confined to latex catheters, however, as similar effects may be seen with PVC catheters where unreacted monomer may be dispersed in the polymer system and diffuse into the surrounding tissues. Rarely, silicone elastomer catheters may be toxic as a result of persistent catalyst on the surface, although toxicity has not yet been observed with catheters made of pure silicone.

Accepting the limitations imposed by the uncontrolled, non-random and retrospective nature of Robertson's research, his results have merely shown that the catheters studied are likely to be of similar

toxicity, although no mention is made of urethritis, and the only endpoint is those patients with symptomatic strictures. The findings of this research do not refer to catheters in general and we believe the broad conclusions reached are unsubstantiated.

It is fortunate that we have not seen a repeat of the high number of catheter-related strictures and urethritis reported between 1979 and 1982. This is due directly to a greater awareness of most clinicians regarding catheter toxicity and an appropriate response from the manufacturers in developing a better product. However, irrespective of the material used in the catheter's manufacture, the potential for toxicity still exists, and toxicity evaluation should be performed according to acceptable standards and the results of the evaluation made available.

Yours faithfully,

J. Nacey and B. Delahunt

Departments of Urology and Pathology, Wellington School of Medicine, Wellington, New Zealand.

Reply from Mr G. S. M. Robertson. Thank you for the opportunity to reply to Drs Nacey and Delahunt's comments on our study. We would agree with their reiteration of our introductory comments on the link between the cytotoxicity of catheter material and the inflammatory response, and the likely (although unproven) link between urethritis and subsequent stricture formation. This has led to the development of a method for testing urinary catheters based on the toxicity of a catheter extract to cells in culture which was published in Australian Standard AS2696, 1984. In the United Kingdom such cytotoxicity tests for medical rubber and plastics were similarly developed and published as BS5736, to which both catheters in our study conformed. It is likely that this, rather than "fortune" is the reason why we have not seen a repeat of the high number of catheter-related strictures reported between 1979 and 1982, and it seems obvious that such toxicity evaluation should continue to occur.

Their major criticism of our study is that our conclusion that "the study provides no evidence that the short-term use of latex catheters is associated with stricture formation" is unjustified. While we included in our discussion the fact that we could only be 90% certain statistically that the true risk of stricture formation due to latex catheters was less than 1.5 times that due to plastic, it seems difficult to draw any other conclusion from a study

in which the stricture rate adjusted for confounding variables was lower in the group with latex catheters (with risk ratio of 0.74:1). The fact that the only endpoint of our study was symptomatic strictures gives it a clinical relevance not present in studies extrapolating from mucosal inflammation in the canine urethra (Nacey *et al. J. Urol.*, **134**, 623–625, 1985), which indeed concluded that “a clinical trial would be the final arbiter in considering the safety of urethral catheters”.

Since all catheters now conform to British Standard 1695: part 2: 1990 and undergo cytotoxicity testing, we stand by our conclusion that the short-term use of such latex catheters seems unlikely to be associated with excessive stricture formation. While we would agree that “cost factors must be held secondary to obtaining a high quality and clinically reliable product” (Nacey and Delahunt. *N.Z. Med. J.*, **104**, 355–356, 1991), in the absence of any evidence that current latex catheters are not such a reliable product, it seems appropriate to include cost in the purchasing decision.

Dear Sir,

re Idiopathic kidney stone formation—where and why? H. L. Chhabra and K. K. Manocha. *Br. J. Urol.*, **68**, 568–570, 1991.

We read with interest the above article on the specific electrical conductance (SEC) of stone formers' urine compared with that of normal individuals. We would, however, like to draw the authors' attention to the following points which we believe cast some doubt on the validity of the results they presented and their rather spurious conclusions.

First, we understand from an earlier paper (Chhabra and Manocha. *Ind. J. Med. Res.*, **81**, 68–70, 1985) that they used a Wheatstone bridge method to measure the SEC of urine at an excitation frequency of 50 Hz. Whilst such a system is perfectly accurate for measuring the electrical resistance of a solid conductor, it is very unreliable when measuring the SEC of a complex solution such as urine. The principal reason for this is that the peaks and troughs of the alternating excitation current have a significant direct component, 20 mS/cycle at 50 Hz. This is sufficient time for dissociation of the solution to occur, thereby inducing considerable errors produced by ionisation of the sample. This effect can to some extent be reduced by the design of the conductivity cell, which should have large surface

area electrodes, although the authors do not include this description in their methodology. Any measurement of the SEC of a solution must, therefore, be conducted with a minimum excitation frequency of 1 kHz and ideally much higher, particularly if the electrode size is reduced.

Second, the authors refer to a paper published previously (Manocha *et al. Ind. J. Med. Res.*, **86**, 124–127, 1987) which studied 24-h urine samples and showed lower SEC values in stone formers than in normals, whereas the specific gravities (SGs) were similar. Extraordinarily, however, they failed to mention 24-h urine volumes; hence their SEC results could be interpreted as meaning any of the following:

1. Stone formers have high urine volumes with high urea content, presumably due to high protein intake, as upper tract stone disease is more prevalent in higher socioeconomic groups.
2. Stone formers have low total urinary salts, presumably due to low dietary intake, perhaps with increased salt losses from sweating or diarrhoea, and a high protein intake.
3. A mixture of the above factors.

Third, the authors claimed to be unable to demonstrate a correlation between SEC and SG. This finding conflicts with the chemical basis on which the SG strips (Ames Multistix SG, Miles Laboratories) were developed, which rely on interpretation of SG from ionic concentration. Cadoff *et al. (J. Urol.*, **139**, 323–325, 1988) demonstrated that the results obtained using similar test strips on stone formers' urine correlated with SG ($r=0.76$). Similarly, Goble (*West Engl. Med. J.*, **106**, 15, 1991) demonstrated a correlation coefficient of 0.94 between SEC and SG in stone formers' urine.

Chhabra and Manocha state in their introduction that the total amount of urinary solute per unit volume is the same in both stone formers and normals, omitting the possibility discussed above that the proportion of ionised and non-ionised components may differ, especially in the light of their methodology. In this paper they only measured SEC in morning samples of urine, so that the results could simply mean that stone formers drink more water, or excrete less salts, due to the reasons listed above. Indeed, Isaacson (*Invest. Urol.*, **5**, 406–413, 1968) demonstrated that the ionic fraction of the total osmolality and the variability of individual ionic constituents in stone formers' urine were very similar to those of normal controls.

Lastly, a mean SEC of 10.24 mS in early morning specimens is an extremely unusual finding. Goble

(*West Engl. Med. J.*, **106**, 15, 1991) demonstrated that 72% of random SEC readings from stone formers' urine were above 14.0 mS ($SG \geq 1.013$) despite prior advice on increasing fluid intake. Similarly, Nauth-Misir *et al.* (unpublished data) found that urine concentrations above 14.0 mS had a propensity to occur in early morning urines, 65% of 607 early morning readings from 22 stone formers, despite the moderate UK climate.

As a result of these observations, we conclude that it is premature to explore theories of why urine conductivity is reduced in stone formers due to some supposed and mysterious change in dielectric constant or other cause.

Yours faithfully,

G. A. Rose and N. M. Goble
52 Uphill Road, London NW7 4PU

Reply from H. L. Chhabra and K. K. Manocha. In reply to Drs Rose and Goble we would like to draw attention to the following facts.

Firstly, we have used the conductivity meter type 305 manufactured by M/S Systronics India Ltd and used for the measurement of conductivity of complex solutions in chemistry departments, particularly physical chemistry. The sample cell size used in this work was 1 cm³ and the cell is in the form of a cube with 1 cm sides which has a fairly large surface area of 1 cm² in comparison with the cross sectional area of wire used in physical work on solid conductors. The electrical field applied across the sample cell is less than 9 volts/cm, which is supposed to be quite low.

The above 2 factors would not have any appreciable effect on the measured value of conductivity due to dissociation of the sample. It is to be further noted that samples of both groups (stone formers and non-stone formers) have been studied under similar physical conditions. Hence the effect of dissociation (or any other for that matter) will be neutralised in a comparative analysis, as pointed out by Dr Rose.

Any effect of frequency other than 50 Hz of the applied field is a subject of separate study due to different relaxation times of multiple ionic and molecular configurations present in the urine of 2 groups. The coefficient of change in SEC with frequency should give an insight into the overall solute structure. The dielectric constants of urine samples of stone formers and non-stone formers have also been measured and agree well with our earlier analytical results. These data have yet to be

published. It is satisfying to note that the results quoted by Drs Rose and Goble in the last paragraph are similar to ours (15 mS or $\leq 1.5 \times 10^4 \mu\text{Mhos}$ for stone formers) even though the quoted measurements have been made without any control of diet and fluid intake, the samples being random.

Dear Sir,

re The use of a bladder pressure warning device during transurethral prostatic resection decreases absorption of irrigation fluid. H. Hjertberg and B. Pettersson. *Br. J. Urol.*, **69**, 56–60, 1992.

Ethanol monitoring is a new method for the detection and quantification of irrigating fluid absorption in transurethral surgery. However, the calculation of the volume of the absorbed irrigant from data on ethanol has raised many questions in hospitals that are starting to use this method. There is a risk of further confusion from the otherwise excellent article by Hjertberg and Pettersson. They use the product of expired-breath values and time to estimate the volume of irrigant absorbed. This procedure has not been validated during TURP. According to pharmacokinetic principles, their approach can be used provided that the *entire* area under the ethanol-time profile is related to the dose of ethanol. On the other hand, validated formulae are available for estimating irrigant absorption which do not require repeated expired-breath tests until zero is reached. The following simple formula, criticised by Hjertberg and Pettersson, has proved very useful in the operating theatre (Hahn. *Acta Anaesthesiol. Scand.*, **33**, 146–151, 1989) and an approximation has also been published in the form of a nomogram (Hahn. *Acta Anaesthesiol. Scand.*, **35**, 557–567, 1991):

Absorption (ml) = 160 + 3210 ethanol in expired air (mg/ml blood equivalent)

This regression equation was based on ethanol monitoring in 60 patients and says that the ethanol concentration in the exhaled breath at any time during TURP corresponds to a certain absorption volume. The factor 160 ml represents the lower limit of detection by the ethanol method (Hahn. *Acta Anaesthesiol. Scand.*, **33**, 146–151, 1989) and makes sense, as several studies have demonstrated that some fluid absorption occurs in every TURP (Hahn. *Acta Anaesthesiol. Scand.*, **35**, 557–567, 1991). For research purposes, however, I would

recommend that either of the 2 existing time-corrected formulae should be used (Hahn. *Acta Anaesthesiol. Scand.*, **33**, 146–151, 1989; Hahn. *Br. J. Urol.*, **68**, 390–393, 1991). These are more complicated but they give a smaller standard error in the estimate of fluid absorption from breath ethanol.

Yours faithfully,

R. G. Hahn

Department of Anaesthesia, Huddinge University Hospital, Huddinge, Sweden.

Reply from Dr H. Hjerterberg. Interest in the absorption of irrigation fluid during TURP is timely despite the development of new methods in treating prostatic obstruction. Dr Hahn is concerned about the possible confusion regarding a formula used to estimate the absorption of ethanol-tagged irrigation fluid. The formula he produced is excellent for clinical use and, as we said in the article, it can be used as a rule of thumb. In fact, we use it every day in the form of a nomogram. It is, however, inexact and provides incorrect values during very slow or very fast absorption. It is also dependent on where in the phase of absorption measurement of ethanol in expired air is made—during the actual absorption, during the equilibration phase, during the linear metabolic phase or during the last phase of the curve. Absorption is also inconstant, irregular in its speed and intermittent, which results in several curves more or less superimposed. This, however, is of no clinical consequence. We require to know if and when absorption takes place, how fast it takes place, if it is without clinical importance or if it is massive, if it continues or ceases, and finally we require a rough estimate of how much the patient has absorbed totally. What is needed is a simple method for detection and a simple nomogram to follow. In our opinion the formula mentioned in fact fulfils all of these criteria. For research purposes we still need a more exact mathematical description of the ethanol kinetics.

Dear Sir,

re Chronic testicular pain following vasectomy. A. J. McMahon, J. Buckley, A. Taylor, S. N. Lloyd, R. F. Deane and D. Kirk. *Br. J. Urol.*, **69**, 188–191, 1992.

In their postal questionnaire the authors record the

incidence of pain to be 33% when assessed 4 years after the operation. It has always been my practice to see all patients 2 or 3 months after vasectomy and a review of patients operated on between 1982 and 1991 may give a different perspective. Records of 186 patients were available. Fourteen patients were not seen post-operatively, giving 172 recordings of the symptom state between 2 and 3 months after operation. Of these, 158 (91.9%) were completely free of pain or discomfort; 4 (2.3%) complained of pain and 10 (5.8%) complained of an occasional slight aching or tenderness (3 only at ejaculation). One patient symptom-free after vasectomy had consulted me 4 years previously for idiopathic testicular pain. Two patients not in this series were both symptom-free at the 3-month follow-up but were referred back to me 2 and 5 years later complaining of disabling testicular pain which they alleged had persisted since their vasectomy operations.

Two conclusions seem to follow. (1) With over 90% of patients being pain-free 2 or 3 months after vasectomy, epididymal distension would appear to be an unlikely cause of post-vasectomy pain. (2) The recommendation that patients should be given prior warning about the possibility of chronic pain after vasectomy should be based on follow-up which does not rely solely on patients' memories.

I am sure that the surgery has not influenced these results but I suspect that the fact that the patients were seen post-operatively by "their" surgeon may have done so.

Yours faithfully,

R. Hole

Department of Urology, South Cleveland Hospital, Middlesbrough.

Reply from Messrs A. J. McMahon et al. I read Mr Hole's comments on our paper with interest. Clearly there are benefits in patients being seen post-operatively by the surgeon performing a vasectomy but I suspect that frequently this is not done, particularly when operations are carried out in a family planning clinic, as was the case with most of our patients. I should like to make the following points.

1. Although the incidence of immediate post-operative complications was dependent on the patient's memory, the long-standing pain was a contemporary symptom present in most of those reporting it at the time of the survey. Thus as far as

this symptom is concerned, follow-up did not "rely solely on patients' memories".

2. It is a feature of this syndrome that the pain often starts some months or even years after the vasectomy. Thus many patients who might subsequently develop the symptom may be pain-free 2 or 3 months after their vasectomy. It is for this very reason that we feel it advisable to warn patients, since this time lapse sometimes means that the patient and his family doctor do not relate the symptom to the vasectomy. Many patients referred to me with this syndrome have been very concerned that some underlying condition, such as cancer, may be causing it. This concern can reinforce what may in itself be a comparatively mild pain and contribute to it becoming intractable.

3. While the aetiology of this syndrome does perhaps still remain a little obscure, I do not think that its late development necessarily excludes epididymal distension as the cause. Recently a patient of mine who was suffering from this syndrome underwent an epididymectomy which demonstrated not only distended tubules in the epididymis but sperm granulomas probably due to extravasation. The latter were, I think, likely to be the cause of his pain and it is not unreasonable to suppose that pre-existing obstructive distension might, after some delay, proceed to produce pain. Although this particular patient is perhaps unusual in having such florid pathology in his epididymis, mild degrees of the same process might well explain the symptoms in some patients.

4. At the time the patients reported in our survey had their vasectomies this syndrome was not clearly recognised and they were not warned of it. Thus it is unlikely that any pre-suggestion has contributed to their symptoms. Both from the survey and from the number of patients referred with this syndrome to our clinics, we feel it to be a definite risk of a procedure which is done for social rather than medical reasons. I understand that even prior to the publication of the results of our survey, a number of medicolegal cases were in the pipeline and I think this reason alone is sufficient to place those performing a vasectomy under an obligation to ensure that patients requesting the operation are aware of the risk, albeit with the reassurance that in the majority of cases the pain is comparatively mild and only rarely requires further medical or surgical intervention.

Dear Sir,

re Conservative treatment of vesicovaginal fistulas by bladder drainage alone. R. J. A. M. Davits and S. I. Miranda. *Br. J. Urol.*, **68**, 155-156, 1991.

The authors of this article report a finding which many urologists have noted at some time or other. The term vesicovaginal fistula (VVF) conventionally implies a well established fistula, but the authors have described 4 cases in which urinary leakage was seen fairly early in the post-operative period. I suggest that these cases should be regarded as delayed or incomplete healing rather than described as a fistula. The authors report that prolonged bladder drainage has ensured complete healing. We too have had several instances of similar success where prolonged catheterisation has helped. It would therefore be interesting to know if Drs Davits and Miranda have tried this method in the treatment of well established cases of VVF. Also, have they treated any further patients in this manner and what was the maximum delay between operation and the day on which the leak was first detected?

Yours faithfully,

R. B. Sabnis
Department of Urology, LTMG Hospital and
LTMM College, Bombay, India.

Reply from Dr R. J. A. M. Davits. We think Dr Sabnis' remarks are very helpful for complete understanding of the topic. We agree with the comment that the cases we treated were not "well established" VVFs, as indicated by the detailed case reports in our article. In answer to Dr Sabnis' questions: in the Netherlands the incidence of VVF complicating gynaecological surgery is low and we have not treated any complication of this kind since writing the article. We have not tried this method of treatment on "well established" VVFs as we think that this is likely to fail because of the epithelialised fistula tract in these patients. We think our method can lead to cure only if applied before epithelialisation has taken place. Therefore we advise insertion of a catheter as soon as possible after detection of the leakage; diversion of the urine might lead to complete healing, whereas persistent urinary leakage will surely lead to a "well established" VVF.

Dear Sir,

re Ethics, logistics and a trial of transurethral versus open prostatectomy. B. J. Jenkins *et al.* *Br. J. Urol.*, **69**, 372–374, 1992.

We read with interest the above article, which provided an interesting and thorough appraisal of the difficulties in choosing between open and transurethral prostatectomy and questioned the need for and ethics of a trial comparing the 2 types of operation. However, no mention was made of the size of the prostate gland, which we feel is an important consideration. Most urologists would agree that for a small fibrous prostate gland a TURP is the operation of choice. However, with larger glands the risks associated with a TURP are obviously increased when the procedure is prolonged (irrigating fluid absorption, blood loss, *etc.*). We consider that in these cases there is a place for an open operation and have recently reviewed our results for the 2 surgical approaches, concentrating on glands larger than 50 g (Lewis *et al.* *Br. J. Urol.*, **69**, 598–602, 1992). We found that of 1289 prostatectomies, performed between January 1985 and December 1989, TURP accounted for 94%. For glands larger than 50 g there were 73 open and 94 transurethral procedures. There was 1 death in each group and overall complication rates were the same, with the higher early complication rate in the open group compensated for by the increased late complication rate in the TUR group. It seems likely that the good short-term results of TURP are largely overshadowed by the increased incidence of late complications such as stricture and "regrowth", both of which require further surgical intervention. We feel that retropubic prostatectomy is still a good operation for the large prostate gland.

Yours faithfully,

N. A. Burgess, D. C. Lewis and P. N. Matthews
Department of Urology, University Hospital of Wales, Cardiff.

Reply from Mr B. J. Jenkins and Professor J. P. Blandy. We thank Mr Burgess and his colleagues for their interest in this paper. It was quite by chance that most of the patients in this series had small prostates, the mean weight of gland resected being 20 g. It was not our intention to suggest that all patients should have a transurethral resection rather than an open prostatectomy. Our aim was to highlight the difficulty of setting up a prospective controlled randomised trial between the 2 proce-

dures. We have always recommended that with a large gland a retropubic prostatectomy is the procedure of choice.

Dear Sir,

re Cavernous haemangioma of the glans penis. S. Khanna. *Br. J. Urol.*, **67**, 332, 1991.

Mr Khanna rightly pointed out that penile haemangiomas are extremely rare. Since experience is limited to a few isolated case reports, their aetiology remains unknown. In our 15 years of paediatric surgical experience we have encountered only 1 case of haemangioma involving the penis and scrotum and it was undoubtedly congenital in origin.



A newborn baby of Chinese descent was found to have a haemangiomatous lesion extending from the glans penis to the adjacent scrotal area (Fig.). The lesion, a mixture of cavernous and capillary elements, continued to enlarge during a 7-year follow-up. The capillary haemangioma responded well to laser treatment and the cavernous element required surgical excision.

Yours faithfully,

W. T. Ng, M. K. Wong and Y. T. Chan
Surgical B Unit, Princess Margaret Hospital, Hong Kong

Notices

British Association of Urological Surgeons

President: J. C. Smith, MS, FRCS

Annual Meeting: Harrogate, 22–25 June 1993

Abstracts of contributions to be considered as either papers, posters or videos by the Programme Sub-Committee of Council should be submitted on the special forms, which will be available from the BAUS Secretariat in October 1992. Completed forms, which should state clearly whether the submission is a paper, a poster or a video, must be returned to the Honorary Secretary by Friday, 8th January 1993.

Abstracts not on the special forms will NOT be considered.

All correspondence to: R. J. Morgan, FRCS, Honorary Secretary, British Association of Urological Surgeons, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

British Association of Urological Surgeons

Autumn Meeting: Taliesin Theatre, University College, Swansea. 9 and 10 October 1992

Friday, 9 October: Urogynaecology.

Saturday, 10 October: Programme of Local Clinical and Scientific Papers.

Further information from: BAUS Secretariat, British Association of Urological Surgeons, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

William Cook Travelling Fellowship

In 1990, William Cook Europe Limited generously offered an annual sum of £3000 to finance a

minimum of three travelling fellowships each year. Candidates must be members of the British Association of Urological Surgeons. Applications should be made to the Honorary Secretary of BAUS by 1 February, giving the following information: the name of the centre to be visited, the reason for the visit and an estimate of the cost of travel and accommodation. Prior agreement to the visit must be obtained from the surgeon/hospital in question.

Applications will be considered by a BAUS Committee. Successful applicants will be required to submit a report on the experience gained in the centre visited.

C.-E. Alken Prize

An endowment fund has been established to further clinical work and research in the field of Urology by presenting an annual award of SwF 10,000 for outstanding scientific endeavours. The award will be for an unpublished work in the field of Urology. An award certificate will also be presented. The prize money may be divided among several contributors.

The papers may be written in either German or English and 3 copies must be submitted by 1 October 1992 to: Stiftungsrat C.-E. Alken-Stiftung, Advokaturbüro Kellerhals & Partner, P.O. Box, CH-3000 Bern 7, Switzerland.

Each submission must be affixed with a code word and must not bear the author's name. In addition, a sealed envelope labelled with the code word is to be included, containing on a separate sheet of paper the author's name and professional standing, together with the code word.

The adjudicators for the award will be the Board of Directors of the endowment fund and their decision will be final.

Diary

1992

- September 14–18 Fifth World Meeting on Impotence and Eighth Symposium on Corpus Cavernosum Revascularization, Milan, Italy. Contact: Organizing Secretariat, OMNIA Meeting and Congressi, Via Senato 18, 20121 Milan, Italy.
- September 15–18 Euro-American Conference on Urological Cancer—Clinical and Biological Progress. Athens, Greece. Contact: Erasmus Conference Centre, International Congress Organizers, 227–229 Kifissias Avenue, Athens 145 62, Greece.
- September 17–18 Seventh Annual Paediatric Urology Course. Selwyn College, Cambridge. Contact: Mr R. H. Whitaker, Department of Urology, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ.
- September 21–23 VIII Andrology Course. Barcelona, Spain. Contact: Secretaría General, Fundación Puigvert, c/. Cartagena 340–350, 08025 Barcelona, Spain. Tel: 34.3 2355614. Fax: 34.3 4559938.
- September 23–25 Polish Association of Urology Annual Meeting. Wroclaw, Poland. Contact: Organizing Committee, Katedra i Klinika Urologii, 50–043 Wroclaw, Pl. 1-Maja 8, Poland. Tel: 347-59. Fax: 254 101.
- October 1–2 Continuing Medical Education and Training in Europe: the Future. London. Contact: Dr M. W. N. Nicholls, Conference Office, c/o Fellowship of Postgraduate Medicine, 6 St Andrew's Place, London NW1 4LB. Tel: (44) (0)71 935 5556. Fax: (44) (0)71 224 3219.
- October 1–3 Annual Meeting of the Swiss Society of Urology. Leysin, Switzerland. Contact: Prof. Dr P. Graber, Clinique de Chirurgie Urologique, Hôpital cantonal, CH-1211 Genève 4, or Prof. Dr D. Hauri, Urologische Klinik, Universitätsspital, CH-8091 Zürich.
- October 1–3 Fourth World Congress of VideoUrology. Monte Carlo, Monaco. Contact: Convergences—VideoUrology '92, 120 Avenue Gambetta, 75020 Paris, France. Telex: 216 911 F. Fax: (33-1) 40 31 01 65.
- October 3 Meeting of the Belgian Association of Urology. Bruges, Belgium. "Early diagnosis and treatment of localized carcinoma of the prostate". Contact: Dr J. Ampe, Department of Urology, A.Z. St Jan, Ruddershove 10, 8000 Brugge, Belgium.
- October 6–9 27th Annual Meeting of Egyptian Urological Association. Alexandria, Egypt. Contact: Dr Mamdouh Koraitim, Department of Urology, Faculty of Medicine, Alexandria University, Alexandria, Egypt.
- October 7–11 1992 Duke Urologic Assembly. "Contemporary Issues in Urology". Pinehurst, North Carolina. Contact: Linda Mace, Assembly Coordinator, Box 3707, Duke Medical Center, Durham, NC 27710, USA.
- October 8–11 International Congress: History, Knowledge & Quality of Life In Urology, Fiuggi, Italy. Contact: Prof. P. Marandola, Università di Pavia, Policlinico S. Matteo, Istituto di Clinica Chirurgica, P. le Golgi 2 27100 Pavia, Italy. Tel: 39 382 423265.
- October 9–10 BAUS Autumn Meeting. Swansea. Contact BAUS Office.

- October 15–16 European School of Oncology. 10th Anniversary Events. Milan, Italy. Contact: European School of Oncology, Via Venezian 18, 20133 Milan, Italy. Tel: (+39 2) 70635923-2364283. Fax: (+39 2) 2664662.
- November 1–4 Third International Workshop on Carcinoma *in situ* and Cancer of the Testis. Copenhagen, Denmark. Contact: Workshop Secretariat, c/o Professor N. E. Skakkebaek, University Department of Growth and Reproduction, Section 5064, Rigshospitalet, 9 Blegdamsvej, DK-2100, Copenhagen, Denmark.
- November 8–10 Fourth International Conference of the Society for Minimally Invasive Therapy. Dublin, Ireland. Contact: Professor J. Fitzpatrick, 47 Eccles Street, Dublin 2, Ireland. Tel: +353-1-308530. Fax: +353-1-300345.
- November 27–28 International Postgraduate Course on Reconstructive Surgery of the Lower Urinary Tract in Children. Amsterdam, The Netherlands. Contact: Conference Secretariat, Bureau PAOG Amsterdam, Tafelbergweg 25, 1105 BC Amsterdam, The Netherlands. Tel: +31 20-566 4801. Fax: +31 20-696 3228.
- December 4–5 Eighth International Steglitz Paediatric Surgical Congress. Berlin, Germany. Contact: Dr F. Schier, Kinderchirurgie, Univ.-Klinikum Steglitz, Hindenburgdamm 30, 1000 Berlin 45, Germany. Tel: (030) 798 4181 or 798 2909; Fax: (030) 798 4141.
- 1993
- January 26–29 Ninth Copenhagen Symposium on Endoscopic Urological Surgery. Herlev, Denmark. Contact: Dr F. Rasmussen, Department of Urology, Herlev Hospital, DK-2730 Herlev, Denmark.
- March 19–20 Second European Congress on Ambulatory Surgery. Brussels, Belgium. Contact: Dr C. De Lathouwer, Brussels One Day Clinic, Avenue du Duc Jean 71–73, B-1080 Brussels, Belgium. Tel: +322/424.1212. Fax: +322/425.7076.
- April 19–22 2nd Interamerican Meeting on Pediatric Urology. Viña Del Mar, Chile. Contact: Dr Ricardo Gonzalez, 420 Delaware Street, S.E. Box 45, University of Minnesota Hospital, Minneapolis, Minnesota 55455, USA. Tel: 612 625-9117. Fax: 612 626-2458 or Dr Ricardo Zubieta, Esmeralda 678, 3 er Piso, Of. 303, Casilla 639, Santiago, Chile. Tel: 56-2-331. Fax: 56-2-391 085.
- May 16–20 American Urological Association, San Antonio Convention Centre, San Antonio, Texas.
- June 20–24 Canadian Urological Association Annual Meeting, Bonaventure Hotel, Montreal, Quebec. Contact: To be announced.
- 1994
- May 15–19 American Urological Association, Moscone Centre, San Francisco, California.

Erratum

**re Vesicosigmoid Fistula as an Incidental Finding
Accompanying Bladder Cancer.** N. E. Stavropoulos
et al.

Br. J. Urol. (1992), **69**, 99.

Please note the following corrections: WBC $14.7 \times 10^6/l$ (not 10^9); RBC $3.96 \times 10^9/l$ (not 10^{12}). The caption for Figure 1 should have been placed under Figure 2 and vice versa.

The publishers apologise for these errors.



SIU REPORTS



**Due for publication in 1992
Based on presentations at
the 22nd Congress of the SIU**

Continent Urinary Diversion

0 443 04645 X

*Edited by Professor R Hohenfellner and Professor R Wammack
Mainz, Germany*

Publication date August 1992

Evaluation of Chemotherapy for Bladder Cancer

0 443 04644 1

*Edited by Professor H Villavicencio
Barcelona, Spain and Professor W R Fair
New York, United States of America*

Publication date November 1992

Urinary Incontinence

0 443 04643 3

*Edited by Professor A Steg and J M Buzelin
Paris, France*

Publication date November 1992

Oncogenes and Molecular Genetics of Urological Tumours

0 443 04646 8

*Edited by Professor C A Olsson
New York, United States of America*

Publication date August 1992

Non-Surgical Treatment of BPH

0 443 04642 5

*Edited by Professor J M Fitzpatrick
Dublin, Ireland*

Publication date August 1992

304 pages, 234 x 156 mm, cased, retail price £50.00 each

Published on behalf of the Société Internationale d'Urologie by Churchill Livingstone

For ordering information, contact **Longman Group UK Ltd, PO Box 88,**

Fourth Avenue, Harlow, Essex CM19 5SR

(tel) 0279-442601

(fax) 0279-444501

Minimally invasive Surgery

Laparoscopic Lymphadenectomy



Examining pelvic lymph nodes can yield information of value in planning the future courses of prostate carcinoma therapies. Minimally invasive laparoscopic lymphadenectomic surgical procedures provide a number of advantages over laparotomic procedures here. Their low patient traumatizations reduce postoperative complications, significantly shortening confinement periods.

KARL STORZ supplies all of the equipment needed for these procedures in high qualities commensurate with the company's impeccable world-wide reputation: autoclavable Hopkins telescopes, complementing surgical instruments specially developed for this application, plus the latest in insufflators and radiofrequency surgery units.

KARL STORZ GMBH & CO.
Mittelstr. 8, Postfach 230
D-7200 Tuttlingen/Germany
Cable: Endoskopie
Phone: (07461) 7080, Telex: 762656 storz d
Telefax: 746 118, Telefax: (07461) 708105

KARL STORZ Endoscopy - America, Inc.
10111 W. Jefferson Boulevard, Culver City,
California 90232-3578, Phone: (213) 558 1500,
Telex: 910-340-6372 k storz culv.
Telefax: 213 280 2504

KARL STORZ Endoscopia Latino-America
815 N.W. 57 AV, Suite No. 342
Miami, Florida 33126
Phone: KSLA (305) 262 - 8980
Telex: 510 601 6506, Telefax: (305) 262 - 8986

United Kingdom agents:



Rimmer Brothers
Aylesbury House
Clerkenwell Green
London
EC1R 0DD
Tel: 071-251 6494

STORZ
KARL STORZ - ENDOSKOPE

Please send me more information.

UPO 24